WEST Search History

DATE: Friday, February 07, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB; PLUR=YES; OP=ADJ		
L9	(mlk same inhib$) and parkinson$ not (l2 or l8)	0	L9
L8	(((mixed or multiple)adj lineage adj kinase) same inhib$) and parkinson$ not l2	3	L8
	DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L7	L6 not l5	0	L7
L6	(((mixed or multiple)adj lineage adj kinase) same inhib$) and parkinson$	3	L6
L5	(mlk same inhib$) and parkinson$	3	L5
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L4	(mlk same inhib$) and parkinson$	10	L4
	DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L3	(mlk same inhib$) and parkinson$ not l1	3	L3
	DB=USPT,PGPB; PLUR=YES; OP=ADJ		
L2	(mlk with inhib$) and parkinson$ not l1	4	L2
	DB=USPT; PLUR=YES; OP=ADJ		
L1	(mlk with inhib$) same parkinson$	1	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Friday, February 07, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ		
L9	(((mixed or multiple) lineage kinase) and inhib$) and @pd<19980514	0	L9
L8	(mlk and inhib$) and @pd<19980514	2	L8
	DB=USPT; PLUR=YES; OP=ADJ		
L7	(mlk and inhib$) and @ad<19980514 not l6	8	L7
L6	(mlk and inhib$) and @pd<19980514	4	L6
L5	(((mixed or multiple) lineage kinase) and inhib$) and @ad<19980514	11	L5
L4	(((mixed or multiple) lineage kinase) and inhib$) and @pd<19980514	0	L4
L3	(((mixed or multiple) lineage kinase) same inhib$) and @pd<19980514	0	L3
L2	(mlk same inhib$) and @pd<19980514	1	L2
L1	(mlk with inhib$) and @pd<19980514	0	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Friday, February 07, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=ADJ		
L3	(kinase with inhibS) and parkinsonS and @pd<19980514	82	L3
L2	(kinase with inhibS same parkinsonS) and @pd<19980514	0	L2
L1	kinase with inhibS and @pd<19980514	1208	L1

END OF SEARCH HISTORY

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* * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *



FILE 'HOME' ENTERED AT 10:48:27 ON 07 FEB 2003

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,
       BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
       CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE,
       DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 10:48:37 ON 07 FEB 2003

64 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF

=> s ((mlk or (mixed lineage kinase) or (multiple lineage kinase))(1)inhib?) and
parkinson?
          1   FILE ADISCTI
          1   FILE ADISINSIGHT
          1   FILE BIOSIS
          1   FILE BIOTECHABS
          1   FILE BIOTECHDS
  13 FILES SEARCHED...
          3   FILE CAPLUS
          1   FILE CIN
  22 FILES SEARCHED...
          1   FILE DDFU
         19   FILE DGENE
          1   FILE DRUGU
          1   FILE EMBASE
  32 FILES SEARCHED...
          1   FILE ESBIOBASE
          1   FILE IFIPAT
  44 FILES SEARCHED...
          1   FILE PHARMAML
          1   FILE PHIN
  54 FILES SEARCHED..
          1   FILE PROMT
          1   FILE TOXCENTER
         21   FILE USPATFULL
  62 FILES SEARCHED...
          5   FILE WPIDS
          5   FILE WPINDEX

  20 FILES HAVE ONE OR MORE ANSWERS,   64 FILES SEARCHED IN STNINDEX

L1   QUE ((MLK OR (MIXED LINEAGE KINASE) OR (MULTIPLE LINEAGE KINASE))(L) INHIB
       ?) AND PARKINSON?

=> d rank
F1          21   USPATFULL
F2          19   DGENE
F3           5   WPIDS
F4           5   WPINDEX
F5           3   CAPLUS
F6           1   ADISCTI
F7           1   ADISINSIGHT
```

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F8              1   BIOSIS
F9              1   BIOTECHABS
F10             1   BIOTECHDS
F11             1   CIN
F12             1   DDFU
F13             1   DRUGU
F14             1   EMBASE
F15             1   ESBIOBASE
F16             1   IFIPAT
F17             1   PHARMAML
F18             1   PHIN
F19             1   PROMT
F20             1   TOXCENTER


=> file f1 f3-20
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       3.85       4.06

FILE 'USPATFULL' ENTERED AT 10:52:31 ON 07 FEB 2003
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FILE 'IFIPAT' ENTERED AT 10:52:31 ON 07 FEB 2003
COPYRIGHT (C) 2003 IFI CLAIMS(R) Patent Services (IFI)
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FILE 'PROMT' ENTERED AT 10:52:31 ON 07 FEB 2003
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FILE 'TOXCENTER' ENTERED AT 10:52:31 ON 07 FEB 2003
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=> s l1
   6 FILES SEARCHED...
  12 FILES SEARCHED...
L2          42 L1

=> dup rem l2
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L2
L3          36 DUP REM L2 (6 DUPLICATES REMOVED)
               ANSWERS '1-21' FROM FILE USPATFULL
               ANSWERS '22-26' FROM FILE WPIDS
               ANSWERS '27-29' FROM FILE CAPLUS
               ANSWER '30' FROM FILE ADISCTI
               ANSWER '31' FROM FILE ADISINSIGHT
               ANSWER '32' FROM FILE BIOTECHDS
               ANSWER '33' FROM FILE CIN
               ANSWER '34' FROM FILE PHARMAML
               ANSWER '35' FROM FILE PHIN
               ANSWER '36' FROM FILE PROMT

=> d bib abs 22-30 32-36

L3   ANSWER 22 OF 36  WPIDS (C) 2003 THOMSON DERWENT
AN   2002-454607 [48]   WPIDS
CR   2002-454608 [48]; 2002-454609 [48]; 2002-479640 [51]; 2002-722778 [78];
     2002-740090 [80]; 2002-740204 [80]; 2002-750045 [81]
DNC  C2002-129276
TI   New protein complex comprising CIB and mixed lineage kinase 2, useful as
     targets for diagnostic tools in identifying individuals at risk for
     neurodegenerative disorders, e.g. Alzheimer's disease, Parkinson
     's disease or dementia.
DC   B04 D16
IN   BARTEL, P L; HEICHMAN, K; ROCH, J
PA   (MYRI-N) MYRIAD GENETICS INC
CYC  97
PI   WO 2002033112 A2 20020425 (200248)* EN   91p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
            RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
     US 2002106773 A1 20020808 (200254)
     AU 2002013239 A  20020429 (200255)
ADT  WO 2002033112 A2 WO 2001-US32196 20011016; US 2002106773 A1 Provisional US
     2000-240790P 20001017, US 2001-973064 20011010; AU 2002013239 A AU
     2002-13239 20011016
FDT  AU 2002013239 A Based on WO 200233112
PRAI US 2000-240790P  20001017; US 2001-973064   20011010
AN   2002-454607 [48]   WPIDS
CR   2002-454608 [48]; 2002-454609 [48]; 2002-479640 [51]; 2002-722778 [78];
```

2002-740090 [80]; 2002-740204 [80]; 2002-750045 [81]

AB WO 200233112 A UPAB: 20021220

NOVELTY - An isolated protein complex (I) comprising two proteins, and selected from:

(a) a complex of calcium binding protein (CIB) and **mixed lineage kinase** 2 (MLK2);

(b) a complex of a fragment of CIB and MLK2;

(c) a complex CIB and a fragment of MLK2; and

(d) a complex of a fragment of CIB and a fragment of MLK2, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated antibody selectively immunoreactive with (I);

(2) diagnosing a neurodegenerative disorder;

(3) determining whether a mutation in a gene encoding one of the proteins of a protein complex (I) is useful for diagnosing a neurodegenerative disorder;

(4) a non-human animal model for a neurodegenerative disorder where the genome of the animal or its ancestor has been modified such that the formation of a protein complex has been altered;

(5) a cell line obtained from the animal model of (4);

(6) a non-human animal model for a neurodegenerative disorder, where the biological activity of a protein complex has been altered;

(7) cell lines in which the genome of cells of the cell line has been modified to produce or eliminate at least one protein complex defined above;

(8) a composition comprising a first expression vector having a nucleic acid encoding CIB or its homologue, derivative or fragment, and a second expression vector having a nucleic acid encoding **MLK** or its homologue, derivative or fragment;

(9) a host cell comprising a first expression vector having a nucleic acid encoding a first protein which is CIB, or its homologue, derivative or fragment, and a second expression vector having a nucleic acid encoding a second protein which is **MLK**, or its homologue, derivative or fragment;

(10) screening drug candidates capable of modulating the interaction of the proteins of a protein complex;

(11) screening for drug candidates useful in treating a neurodegenerative disorder;

(12) a drug useful for treating a neurodegenerative disorder identified by the method in (11);

(13) selecting modulators of a protein complex formed from or between a first protein and a second protein;

(14) selecting modulators of an interaction between a first polypeptide and a second polypeptide;

(15) selecting modulators of **MLK**;

(16) a modulator useful for treating a neurodegenerative disorder identified by the methods above;

(17) identifying a compound that binds to **MLK** in vitro;

(18) a compound useful for treating a neurodegenerative disorder identified in (17);

(19) providing **inhibitors** of an interaction between a first polypeptide and a second polypeptide;

(20) an **inhibitor** useful for treating a neurodegenerative disorder identified in (19);

(21) modulating in a cell a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**;

(22) modulating the interaction of **MLK** with a ligand in a cell;

(23) modulating neuronal death in a patient having a neurodegenerative disorder;

(24) treating a neurodegenerative disorder; and

(25) modulating MLK activity or MLK activities of a protein in a cell.

ACTIVITY - Neuroprotective; Nootropic; Antiparkinsonian; Anticonvulsant.

MECHANISM OF ACTION - CIB-mixed lineage kinase 2 protein complex modulator. No supporting data is given in the source material

USE - The AD interacting proteins are useful as new targets for the identification of useful pharmaceuticals, new targets for diagnostic tools in the identification of individuals at risk, sequences for producing transformed cell lines, cellular models and animal models, and new bases for therapeutic intervention in neurodegenerative disorders, particularly AD. The proteins and DNA encoding the proteins may also be used in the development of diagnostic and therapeutic tools against AD. Modulators of the protein complex are useful for treating a neurodegenerative disorder including Huntington's disease, Parkinson's disease, dementia or Alzheimer's disease.

Dwg.0/0

L3 ANSWER 23 OF 36 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-519067 [55] WPIDS
DNC C2002-146743
TI New fused pyrrolocarbazoles useful in the treatment of e.g. prostate disorders.
DC B02
IN GINGRICH, D E; HUDKINS, R L
PA (CEPH-N) CEPHALON INC; (GING-I) GINGRICH D E; (HUDK-I) HUDKINS R L
CYC 97
PI WO 2002017914 A2 20020307 (200255)* EN 64p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001085205 A 20020313 (200255)
US 2002061920 A1 20020523 (200255)
ADT WO 2002017914 A2 WO 2001-US26266 20010823; AU 2001085205 A AU 2001-85205 20010823; US 2002061920 A1 Provisional US 2000-227803P 20000825, Provisional US 2001-278455P 20010323, US 2001-935285 20010822
FDT AU 2001085205 A Based on WO 200217914
PRAI US 2001-935285 20010822; US 2000-227803P 20000825; US 2001-278455P 20010323
AN 2002-519067 [55] WPIDS
AB WO 200217914 A UPAB: 20020829
NOVELTY - Fused pyrrolocarbazoles are new.

DETAILED DESCRIPTION - Fused pyrrolocarbazoles of formula (I) are new.

R1 and R2 = H or 1-8C alkyl (substituted by -OH or -OR4);

R4 = 1-4C alkyl, aryl or residue of an amino acid after the hydroxy group of carboxyl is removed;

R3 = -CH2OH, -CH2OR7, -(CH2)nSR5, -(CH2)nS(O)yR5, -CH2SR5 or 1-8C alkyl (substituted by -OH, -OR5, -OR8, -CH2OR7, -S(O)yR6 or -SR6);

R5 = 1-4C alkyl or aryl;

R6 = H, 1-4C alkyl or 6-10C aryl;

R7 = H or 1-4C alkyl;

R8 = residue of an amino acid after the hydroxyl group of the carboxyl is removed;

n = 1 - 4; and

y = 1 or 2.

ACTIVITY - Cytostatic; Gynecological; Antidiabetic; Ophthalmological; Antipsoriatic; Antirheumatic; Antiarthritic; Antiarteriosclerotic; Vasotropic; Nootropic; Neuroprotective; Antiparkinsonian; Cerebroprotective; Anticonvulsant; Anti-HIV; Antiinflammatory.

MECHANISM OF ACTION - Vascular Endothelial Growth Factor Receptor Kinase (VEGFR) **Inhibitor**; **Mixed Lineage Kinase** (**MLK**)-1 **Inhibitor**; **MLK**-2 **Inhibitor**; **MLK**-3 **Inhibitor**; trkA Tyrosine Kinase **Inhibitor**; NGF-stimulated trk Phosphorylation and Platelet Derived Growth Factor Receptor (PDGF beta) **inhibitor**.

9-ethoxymethyl-12-(3-hydroxypropyl)-6,7,12,13-tetrahydro-5H-pyrrolo(3,4-c)carbazole(1,2-a)inden-5-one was examined for the **inhibitory** effects on the kinase activity of baculovirus-expressed VEGF receptor kinase domain using the procedure described by Angeles et al., Anal. Biochem. 236:49-55, 1996. The results indicated a 50% **inhibitory** concentration (IC50) value of 4 nM.

USE - For the treatment or prevention of prostrate, angiogenic, pathological, neurodegenerative, multiple myeloma and leukemia disorders e.g. prostate cancer, benign prostate hyperplasia, cancer of solid tumors, ocular disorder, macular degeneration, endometriosis, diabetic retinopathy, psoriasis, hemangioblastoma, neoplasia, rheumatoid arthritis, chronic arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, atherosclerosis, restenosis, Alzheimer's disease, amyotrophic lateral sclerosis, **Parkinson**'s disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, chemotherapy induced peripheral neuropathy, AID related peripheral neuropathy, injuries of brain or spinal chord, acute/chronic myelogenous leukemia, and acute/chronic lymphocytic leukemia (all claimed). Also useful for the **inhibition** of c-met, c-kit, and mutated Flt-3 containing internal tandem duplications in the juxtamembrane domain, disease associated with apoptotic cell death of the central nervous system, immune system and inflammatory diseases. The compounds can also be used in the development of in vitro models of neuronal cell survival, function, identification or for screening other synthetic compounds having activities similar to isomeric fused pyrrolocarbazole and isoindolones. Also useful in **inhibition** of angiogenesis, antitumor agent, enhancing the function and/or survival of cells of neuronal lineage, either singularly or in combination with neurotrophic factor and/or indolocarbozoles, enhancing trophic factor-induced activity, **inhibition** of kinases, **inhibition** of vascular endothelial growth factor receptor (VEGFR) kinase, **inhibition** of **mixed lineage** **kinase**, trk kinase, **inhibition** of platelet derived growth factor receptor kinase, **inhibition** of NGF-stimulated trk phosphorylation, **inhibition** of protein kinase C activity, **inhibition** of trk tyrosine kinase activity, **inhibition** of proliferation of prostate cancer cell-line, **inhibition** of the cellular pathways involved in the inflammation process, enhancement of survival neuronal cells at risk of dying.

Dwg.0/0

L3 ANSWER 24 OF 36 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-304059 [34] WPIDS
DNC C2002-088410
TI Identifying a compound useful in the treatment of AIDS peripheral neuropathy comprises contacting a cell containing a multiple linkage kinase protein with a compound and determining if the compound decreases protein activity.
DC B02 B04 D16
IN DIONNE, C A; GLICKSMAN, M A; KNIGHT, E; MAHONEY, A; NEFF, N; WALTON, K M
PA (CEPH-N) CEPHALON INC
CYC 95
PI WO 2002014536 A2 20020221 (200234)* EN 114p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001083179 A 20020225 (200245)
ADT WO 2002014536 A2 WO 2001-US24822 20010808; AU 2001083179 A AU 2001-83179 20010808
FDT AU 2001083179 A Based on WO 200214536
PRAI US 2000-637054 20000811
AN 2002-304059 [34] WPIDS

AB WO 200214536 A UPAB: 20020528
NOVELTY - Identifying a compound (I), which is useful in the treatment of AIDS peripheral neuropathy, involves contacting a cell or cell extract containing a multiple linkage kinase (**MLK**) protein with (I) and determining whether (I) decreases or **inhibits** activity of the **MLK** protein.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for treating a human having AIDS peripheral neuropathy by administering (I).

ACTIVITY - Cytostatic; Gynecological; Opthalmological; Antipsoriatic; Antiinflammatory; Analgesic; Antirheumatic; Antiarthritic; Vulnerary; Cardiant; Antiarteriosclerotic; Vasotropic; Antiparkinsonian; Nootropic; Neuroprotective; Antidiabetic; Anticonvulsant.

Cerebral cortices were dissected from embryonic day 18 rat fetuses and enzymatically digested to obtain a single cell suspension. Cells were seeded at a density of 1.56 multiply 105/cm2 onto poly-ornithine/laminin coated 96 well tissue culture plates in serum-free neural basal medium containing B27 supplements. Plates were coated with a solution of poly-ornithine/laminin (8 micro g/ml each) made in PBS for at least 2 hours at 37 deg. C. On in vitro days 5-7, cortical neurons were exposed to Ab25-35 (20 micro M) either in the presence or absence of a compound of formula (Ic'). Ab25-35 (1 mM) were prepared in deionized-distilled sterile H2O. Relative neuronal survival was determined at 48 hours post-peptide addition using lactate dehydrogenase (LDH) release as an indicator of plasma membrane integrity viability. Data was expressed as percent **inhibition** of LDH released relative to culture treated with AB25-35 alone. The results obtained were as follows: cortical neurons survival (%) control at 250 nm = 46, 56; motoneurons survival (%) control at 250 nm = 300; mononeurons (%) JNK **inhibition** at 500 nm = 65; Cos-7 cells DLK (%) JNK **inhibition** at 500 nm = 63, 73; Cos-7 cells **MLK**-3 (%) JNK **inhibition** at 500 nm = 98, 99; Cos-7 cells **MLK**-2 (%) JNK **inhibition** at 500 nm = 89, 67; and Cos-7 cells MLK1 (%) JNK **inhibition** at 500 nm = 97, 96.

MECHANISM OF ACTION - Multiple linkage kinase protein **inhibitor**; **Multiple lineage kinase** protein modulator.

USE - For identifying a compound useful in the treatment of AIDS peripheral neuropathy and for treatment of AIDS peripheral neuropathy, in a human (claimed), and for the treatment of diseases involving angiogenesis such as cancer of solid tumors, endometriosis, diabetic retinopathy, psoriasis, hemangioblastoma, as well as other ocular diseases and cancers, solid tumors, neoplasia, inflammatory pain, rheumatoid arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, diseases with cardiovascular end points such as atherosclerosis, restenosis, post-angioplasty restenosis and variety of neurological disorders such as Alzheimer's disease, motor neuron disorder (e.g. amyotrophic lateral sclerosis), **Parkinson**'s disease, cerebrovascular disorder (e.g. stroke, ischemia), Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathies (e.g. those affecting DRG neurons in chemotherapy-associated peripheral neuropathy) including diabetic neuropathy and AIDS peripheral neuropathy; disorders induced by excitatory amino acids; and disorders associated with concessive or penetrating injuries of the brain or spinal cord.

ADVANTAGE - The compounds promotes either cell survival or cell death.

Dwg.0/23

L3 ANSWER 25 OF 36 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-389716 [41] WPIDS
DNC C2001-118750
TI New heterocyclic substituted pyrazolone derivatives are kinase inhibitors, useful for treating or preventing angiogenic disorders, e.g. cancer, endometriosis, diabetic retinopathy, psoriasis.
DC B02 B03
IN SINGH, J; TRIPATHY, R
PA (CEPH-N) CEPHALON INC

CYC 95
PI WO 2001032653 A1 20010510 (200141)* EN 138p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001015811 A 20010514 (200149)
NO 2002002095 A 20020611 (200252)
EP 1226141 A1 20020731 (200257) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6455525 B1 20020924 (200266)
KR 2002063179 A 20020801 (200308)
SK 2002000617 A3 20030109 (200309)
ADT WO 2001032653 A1 WO 2000-US30226 20001101; AU 2001015811 A AU 2001-15811 20001101; NO 2002002095 A WO 2000-US30226 20001101, NO 2002-2095 20020502; EP 1226141 A1 EP 2000-978338 20001101, WO 2000-US30226 20001101; US 6455525 B1 Provisional US 1999-163377P 19991104, US 2000-702191 20001031; KR 2002063179 A KR 2002-705807 20020504; SK 2002000617 A3 WO 2000-US30226 20001101, SK 2002-617 20001101
FDT AU 2001015811 A Based on WO 200132653; EP 1226141 A1 Based on WO 200132653; SK 2002000617 A3 Based on WO 200132653
PRAI US 2000-702191 20001031; US 1999-163377P 19991104
AN 2001-389716 [41] WPIDS
AB WO 200132653 A UPAB: 20010724
NOVELTY - Heterocyclic substituted pyrazolone derivatives (I) are new.
DETAILED DESCRIPTION - Heterocyclic substituted pyrazolone derivatives of formula (I) and their salts are new.
Het = a heterocycle;
R1 = H; 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl or heterocycle, each optionally substituted with 1-5 R6; NRaRa, C(=O)Rb, C(=O)NHRa or CO2Rc;
R2, R3 = H; 1-2C alkyl substituted with 1-5 R6; 3-10C alkyl optionally substituted with 1-5 R6; 2-8C alkenyl optionally substituted with 1-5 R6; 2-6C alkynyl; Cl; Br; I; CN; (CH2)rNRaRa; (CH2)rORc; (CH2)rSRc; (CH2)rC(=O)Rb; (CH2)rCO2Rc; (CH2)rOC(=O)Rb; (CH2)rC(=O)NRaRa; (CH2)rNRaC(=O)Rb; (CH2)rNRaC(=O)ORb; (CH2)rOC(=O)NHRa; (CH2)rNRaS(=O)2Rb; (CH2)rS(=O)2NRaRa; (CH2)rS(O)pRb; or (CH2)rcarbocycle or (CH2)rheterocycle, each optionally substituted with 1-5 R4; or
R2+R3 together may form = heterocycle optionally substituted with 1-4 R4, provided that the heterocycle is other than 2-furanyl; or may form a heterocycle optionally substituted with 1-4 R4, provided that the heterocycle is other than 2-thiazolidinyl or 5-methyl-2-oxazolidinyl;
R4 = H, F, Cl, Br, I, CN, CF3, CF2CF3, NO2, OH, NRaRa, ORc, C(=O)Rb, CO2Rc, OC(=O)Rb, NRaC(=O)Rb, C(=O)NRaRa, OC(=O)NRaRa, NRaC(=O)ORb, NRaS(=O)2Rb, S(=O)2NRaRa, NRaC(=S)Rb, C(=S)NRaRa, NRaC(=O)NRaRa, NRaC(=S)NRaRa, CH=NORc, CH=NRa, CH=NNRaRa, (CH2)rS(O)pRb, O(CH2)qNRaRa, O(CH2)qORc, (CH2)rORd, (CH2)rC(=O)Rd', (CH2)rNHRd, (CH2)rS(O)pRd'; or 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, carbocycle or heterocycle, each optionally substituted with 1-5 R6;
R5 = absent or H, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)r(3-6C cycloalkyl) or (CH2)rphenyl;
R6 = 2-8C alkenyl, 2-8C alkynyl, F, Cl, Br, I, CN, CF3, CF2CF3, NO2, CN, NRfRf, ORf, C(=O)Rf, CO2Rf, OC(=O)Rg, NRfC(=O)Rf, C(=O)RfRf, OC(=O)NRfRf, NReC(=O)ORg, NReS(=O)2Rg, S(=O)2NRfRf, NRaC(=S)Rg, C(=S)NRfRf, NRfC(=O)NRfRf, NRfC(=S)NRfRf, CH=NORe, CH=NRe, CH=NNReRe, S(O)pRf, O(CH2)pNRfRf, O(CH2)pORf, ORd, NHRd, C(=O)Rd', S(O)pRd', P(=O)(ORc)2; or 1-6C alkyl, carbocycle or heterocycle, each optionally substituted with 1-5 Rh; or a 5-7C monosaccharide where each hydroxyl of the monosaccharide is optionally replaced by H, 1-4C alkyl, 1-4C alkoxy or OC(=O)(1-4C alkyl);
Ra = H; or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)r(3-6C cycloalkyl) or (CH2)rphenyl, each optionally substituted with 1-5 Rh; or 2 Ra together may form (CH2)qO(CH2)q, (CH2)qS(CH2)q or (CH2)m, each

optionally substituted with 1-5 Rh;
Rb = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)rphenyl or (CH2)rheterocycle, each optionally substituted with 1-5 Rh;
Rc = H; or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl or (CH2)rphenyl, each optionally substituted with 15 Rh;
Rd = the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;
Rd' = the residue of an amino acid after the hydrogen of the amine is removed;
Re = H or 1-6C alkyl;
Rg = 1-6C alkyl or (CH2)rphenyl, each optionally substituted with 1-5 Rh;
Rf = Rg or H;
Ri = F, Cl, Br, I, OH, NO2, CN, CF3, CF2CF3, 1-4C alkyl, 2-6C alkenyl, 2-6C alkynyl, alkoxy, 3-7C cycloalkyl, carboxyl, formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl, hexanoyl, acetamido, acetate, carbamyl, carboxy, NH2, mono- or dialkylamino, phenyl, benzyl or phenethyl;
Rh = Ri or naphthyl, heterocycle or keto;
m = 2-5;
n = 0-5;
p = 0-2;
q = 1-4; and
r = 0-4.
With the Proviso that:
(i) when R1 and Het are both 2-pyridinyl, R2 and R3 are other than 4-diethylamino-2-phenyl;
(ii) when R1 is 4-carboxy-phenethyl, Het and either R2 or R3 are not both dimethylamino-thiophene;
(iii) R2 and R3 are not both H or both SCH3; and
(iv) when R2 is H and R3 is phenyl, Het is other than 2-furanyl.
ACTIVITY - Cytostatic; gynecological; antidiabetic; ophthalmological; antipsoriatic; nootropic; neuroprotective; antiparkinsonian; cerebroprotective; vasotropic; anticonvulsant; osteopathic; antiinflammatory; immunosuppressive; anti-HIV; virucide.
MECHANISM OF ACTION - Kinase inhibitor.
Tests were carried out to determine inhibition of activity of e.g.:
(a) vascular endothelial growth factor receptor-1 kinase;
(b) trkA tyrosine kinase;
(c) mixed lineage kinase-1; and
(d) fibroplast growth factor receptor kinase (FGFR).
Results for % inhibition for 4-(indol-3-ylmethylene)-3-(1,3-thiazol-2-yl)-2 pyrazolin-5-one (1 micro M) were:
(a) 66 %;
(b) 65 %;
(c) 11 %; and
(d) 52 %.
USE - For treating or preventing angiogenic disorders, e.g. cancer of solid tumors, endometriosis, diabetic retinopathy, psoriasis, hemangioblastoma, ocular disorders or macular degeneration; also Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, injuries of the brain or spinal chord, cancer, restenosis, osteoporosis, inflammation, viral infections, bone or hematopoietic disease, autoimmune diseases or transplant rejection. (I) can be administered with other active agents.
Dwg.0/0

L3 ANSWER 26 OF 36 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-565279 [52] WPIDS
DNC C2000-168346
TI Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives as protein kinase inhibitors useful for treating and preventing e.g. prostate disorders, Alzheimer's disease, AIDS dementia or epilepsy.
DC B02

IN HUDKINS, R L; REDDY, D; SINGH, J; TRIPATHY, R; UNDERINER, T L
PA (CEPH-N) CEPHALON INC
CYC 90
PI WO 2000047583 A1 20000817 (200052)* EN 131p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000033604 A 20000829 (200062)
NO 2001003887 A 20011011 (200174)
EP 1165562 A1 20020102 (200209) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001102085 A 20011115 (200231)
BR 2000008056 A 20020409 (200232)
SK 2001001129 A3 20020404 (200232)
HU 2001005363 A2 20020628 (200255)
CN 1350537 A 20020522 (200258)
CZ 2001002878 A3 20020814 (200263)
ADT WO 2000047583 A1 WO 2000-US3476 20000211; AU 2000033604 A AU 2000-33604 20000211; NO 2001003887 A WO 2000-US3476 20000211, NO 2001-3887 20010809; EP 1165562 A1 EP 2000-911759 20000211, WO 2000-US3476 20000211; KR 2001102085 A KR 2001-710212 20010811; BR 2000008056 A BR 2000-8056 20000211, WO 2000-US3476 20000211; SK 2001001129 A3 WO 2000-US3476 20000211, SK 2001-1129 20000211; HU 2001005363 A2 WO 2000-US3476 20000211, HU 2001-5363 20000211; CN 1350537 A CN 2000-803647 20000211; CZ 2001002878 A3 WO 2000-US3476 20000211, CZ 2001-2878 20000211
FDT AU 2000033604 A Based on WO 200047583; EP 1165562 A1 Based on WO 200047583; BR 2000008056 A Based on WO 200047583; SK 2001001129 A3 Based on WO 200047583; HU 2001005363 A2 Based on WO 200047583; CZ 2001002878 A3 Based on WO 200047583
PRAI US 2000-500849 20000210; US 1999-119834P 19990212
AN 2000-565279 [52] WPIDS
AB WO 200047583 A UPAB: 20011129
NOVELTY - Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives (I) are new.
DETAILED DESCRIPTION - Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives of formula (I) are new.
B', F' = a) an unsaturated 6-membered carbocyclic aromatic ring in which from 1 to 3 carbon atoms may be replaced by nitrogen atoms; b) an unsaturated 5-membered carbocyclic aromatic ring; and c) an unsaturated 5-membered carbocyclic aromatic ring in which either 1) one carbon atom is replaced with an oxygen, nitrogen, or sulfur atom; 2) two carbon atoms are replaced with a sulfur and a nitrogen atom, an oxygen and a nitrogen atom, or two nitrogen atoms; or 3) three carbon atoms are replaced with three nitrogen atoms;
R1 = 1-4C alkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl (all optionally substituted), H, -C(O)R9, -OR10, C(O)NH2, -NR11R12, -(CH2)pNR11R12, -(CH2)pOR10, -O(CH2)pOR10 or -O(CH2)pNR11R12;
R3-R6 = H, aryl, heteroaryl, halo, -CN, -CF3, -NO2, -OH, -OR9, -O(CH2)pNR11R12, -OC(O)R9, -OC(O)NR11R12, -O(CH2)pOR10, -CH2OR10, -NR11R12, -NR10S(O)2R9, -NR10C(O)R9, -CH2OR14, -NR10C(O)NR11R12, -CO2R2, -C(O)R2, -C(O)NR11R12, -CH=NOR2 , -CH=NR9, -(CH2)pNR11R12, -(CH2)pNHR14, -CH=NNR2R2A, -S(O)yR2, -(CH2)pS(O)yR9, -CH2S(O)yR14; or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl (all optionally substituted with 1-3 T)
Q = O, S, NR13, NR7, CHR15, X3CH(R15), and CH(R15)X3; and
W' = CR18R7 or CHR2;
A1, B1 = H;
A2, B2 = H, OR2, SR2 or N(R2)2; or
A1 + A2, B1 + B2 = =O, =S or =NR2; provided that at least one of A1 + A2, or B1 + B2, form =O.
The full definition is given in DEFINITION (Full Definition) field.
ACTIVITY - Cytostatic; antirheumatic; antiarthritic;

cerebroprotective; neuroprotective; vulnerary; antiarteriosclerotic; nootropic; antiparkinsonian; vasotropic; anticonvulsant; antiinflammatory; gynecological; antipsoriatic; ophthalmological; antidiabetic; osteopathic; virucidal; immunosuppressive. Compounds (I) have IC50 of 8-555 nM (% **inhibition** at 300 nM) as measured in an ELISA-based assay for determining the ability of (I) to **inhibit** the kinase activity of baculovirus-expressed human trkA cytoplasmic domain.

MECHANISM OF ACTION - Kinase **inhibitor** such as tyrosine (trkA) kinase, vascular growth factor receptor (VEGFR) kinase, **mixed lineage kinase** (**MLK**) or fibroplast growth receptor (FGFR) kinase **inhibitors**.

USE - (I) are useful for treating and preventing prostate disorders (e.g. prostate cancer or benign prostate hyperplasia), neoplasia, rheumatoid arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, atherosclerosis, Alzheimer's disease, amyotropic lateral sclerosis, **Parkinson**'s disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, injuries of the brain or spinal cord, inflammation, cancer (e.g. solid tumors or a hematopoietic or lymphatic malignancy), endometriosis, psoriasis, hemangioblastoma or ocular disease (e.g. diabetic retinopathy), restenosis, osteoporosis, angiogenesis, viral infections, autoimmune diseases or transplant rejection.

Dwg.0/0

L3 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
AN 2002:1465 CAPLUS
DN 136:363246
TI Mixed lineage kinase activity of indolocarbazole analogues
AU Murakata, Chikara; Kaneko, Masami; Gessner, George; Angeles, Thelma S.; Ator, Mark A.; O'Kane, Teresa M.; McKenna, Beth Ann W.; Thomas, Beth Ann; Mathiasen, Joanne R.; Saporito, Michael S.; Bozyczko-Coyne, Donna; Hudkins, Robert L.
CS Kyowa-Hakko Kogyo Co., Ltd., Tokyo, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(2), 147-150
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB The MLK1-3 activity for a series of analogs of the indolocarbazole K-252a is reported. Addn. of 3,9-bis-alkylthiomethyl groups to K-252a results in potent and selective **MLK inhibitors**. The in vitro and in vivo neuronal survival promoting activity of bis-isopropylthiomethyl-K-252a (CEP-11004/KT-8138) is reported. CEP-11004 demonstrated protection of the JNK kinase pathway following treatment of cells with MPP+ and demonstrated in vivo protection of dopaminergic terminals with the striatum projecting from neurons within the substantia nigra om mice following administration of MPTP. Thus, **inhibition** of **MLKs** may be an effective strategy for blocking neurodegeration assocn. with **Parkinson**'s disease.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
AN 2002:394536 CAPLUS
DN 137:304091
TI Mixed lineage kinase family, potential targets for preventing neurodegeneration
AU Maroney, Anna C.; Saporito, Michael S.; Hudkins, Robert L.
CS Cephalon Inc., West Chester, PA, 19380, USA
SO Current Medicinal Chemistry: Central Nervous System Agents (2002), 2(2), 143-155
CODEN: CMCCCO; ISSN: 1568-0150
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English

AB A review. The c-Jun amino terminal kinase (JNK) cascade leading to c-Jun phosphorylation has been implicated in the neuronal cellular response to a variety of external stimuli including free radical oxidative stress, trophic withdrawal, amyloid toxicity and activation by death domain receptor ligands. Although the exact causes of neuronal loss in neurodegenerative diseases remain unknown, it has been hypothesized that response to these environmental stresses may be contributing factors. Agents which block the JNK signaling cascade have been proposed as a therapeutic approach for preventing neuronal cell death obsd. in a variety of neurodegenerative diseases including **Parkinson**'s, Huntington's, and Alzheimer's disease. The JNKs are regulated through a sequential signaling cascade by a series of upstream kinases including the **mixed lineage kinases** (**MLKs**). Herein, we review the **MLK** family as a therapeutic target and provide evidence with CEP-1347, the most advanced **MLK** **inhibitor** currently in clin. trails for **Parkinson**'s disease, that intervention at the **MLK** point in the JNK cascade may reduce the susceptibility of neurons to degenerate.
RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2003 ACS
AN 2002:41807 CAPLUS
DN 137:163005
TI Inhibitors of the JNK signaling pathway
AU Harper, Sarah J.; LoGrasso, Philip
CS Department of Pharmacology, Neuroscience Research Centre, Harlow, Essex, CM20 2QR, UK
SO Drugs of the Future (2001), 26(10), 957-973
CODEN: DRFUD4; ISSN: 0377-8282
PB Prous Science
DT Journal; General Review
LA English
AB A review. A review on some endogenous **inhibitors** of the jun-N-terminal kinase (JNK) pathway, such as growth factors, JNK-interacting proteins and heat shock protein 72. Various chem. **inhibitors** of the JNK pathway, such as CEP-1347, a **mixed** **-lineage kinase** (**MLK**) **inhibitor**, SB-203580 and SB-202190, combined p38 and JNK **inhibitors** and SPC0009766, are also discussed. The JNK signal transduction pathwy is activated in different cell types and in response to different stressful stimuli. **Inhibition** of JNK promotes cell survival, particularly in neurons. The best prospects for JNK **inhibitors** in the clinic would be for a neuronal target such as stroke or **Parkinson**'s disease, where a specific JNK3 **inhibitor** could be given wihtout effects on non-neuronal cells.
RE.CNT 157 THERE ARE 157 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 36 ADISCTI COPYRIGHT 2003 (ADIS)
AN 2003:430 ADISCTI
DN 800931592
TI CEP-1347 in **Parkinson**'s disease: a pilot study.
ADIS TITLE: CEP 1347: adverse reactions.
Various toxicities
In patients with **Parkinson**'s disease.
AU Schwid S R; Parkinson Study Group.
CS Rochester, New York, USA.
SO Movement Disorders (Jan 1, 2002), Vol. 17 (Suppl. 5), pp. 91
DT Study
RE Neurological Disorders| Parkinson's Disease and Movement Disorders
FS Summary
LA English
WC 438

L3 ANSWER 32 OF 36 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 2002-16970 BIOTECHDS
TI New protein complex comprising CIB and mixed lineage kinase 2, useful as targets for diagnostic tools in identifying individuals at risk for neurodegenerative disorders, e.g. Alzheimer's disease, **Parkinson**'s disease or dementia;
useful for Huntington chorea, **Parkinson** disease, dementia, and Alzheimer disease gene therapy and diagnosis
AU ROCH J; BARTEL P L; HEICHMAN K
PA MYRIAD GENETICS INC
PI WO 2002033112 25 Apr 2002
AI WO 2000-US32196 17 Oct 2000
PRAI US 2000-240790 17 Oct 2000
DT Patent
LA English
OS WPI: 2002-454607 [48]
AN 2002-16970 BIOTECHDS
AB DERWENT ABSTRACT:
NOVELTY - An isolated protein complex (I) comprising two proteins, and selected from: (a) a complex of calcium binding protein (CIB) and **mixed lineage kinase** 2 (MLK2); (b) a complex of a fragment of CIB and MLK2; (c) a complex CIB and a fragment of MLK2; and (d) a complex of a fragment of CIB and a fragment of MLK2, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated antibody selectively immunoreactive with (I); (2) diagnosing a neurodegenerative disorder; (3) determining whether a mutation in a gene encoding one of the proteins of a protein complex (I) is useful for diagnosing a neurodegenerative disorder; (4) a non-human animal model for a neurodegenerative disorder where the genome of the animal or its ancestor has been modified such that the formation of a protein complex has been altered; (5) a cell line obtained from the animal model of (4); (6) a non-human animal model for a neurodegenerative disorder, where the biological activity of a protein complex has been altered; (7) cell lines in which the genome of cells of the cell line has been modified to produce or eliminate at least one protein complex defined above; (8) a composition comprising a first expression vector having a nucleic acid encoding CIB or its homologue, derivative or fragment, and a second expression vector having a nucleic acid encoding **MLK** or its homologue, derivative or fragment; (9) a host cell comprising a first expression vector having a nucleic acid encoding a first protein which is CIB, or its homologue, derivative or fragment, and a second expression vector having a nucleic acid encoding a second protein which is **MLK**, or its homologue, derivative or fragment; (10) screening drug candidates capable of modulating the interaction of the proteins of a protein complex; (11) screening for drug candidates useful in treating a neurodegenerative disorder; (12) a drug useful for treating a neurodegenerative disorder identified by the method in (11); (13) selecting modulators of a protein complex formed from or between a first protein and a second protein; (14) selecting modulators of an interaction between a first polypeptide and a second polypeptide; (15) selecting modulators of **MLK**; (16) a modulator useful for treating a neurodegenerative disorder identified by the methods above; (17) identifying a compound that binds to **MLK** in vitro; (18) a compound useful for treating a neurodegenerative disorder identified in (17); (19) providing **inhibitors** of an interaction between a first polypeptide and a second polypeptide; (20) an **inhibitor** useful for treating a neurodegenerative disorder identified in (19); (21) modulating in a cell a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**; (22) modulating the interaction of **MLK** with a ligand in a cell; (23) (24) modulating neuronal death in a patient having a neurodegenerative disorder; (25) treating a neurodegenerative disorder; and (26) modulating **MLK** activity or **MLK** activities of a protein in a cell.

WIDER DISCLOSURE - Also disclosed as new are protein complexes of: (1) nucleic acids encoding (I) (2) human leukocyte antigen (HLA)-B

associated transcript (BAT3) and glypican interaction; (3) BAT3-LRP2 interaction; (4) BAT3-LRPAP1 interaction; (5) BAT3-transthyretin interaction; (6) Fe65-PN7740 interaction; (7) Min1-GS interaction; (8) Mint1-KIAA0426 interaction; (9) PS1-Mint1 interaction; (10) CASK (post-synaptic protein of MAGUK family)-Dystrophin interaction; (11) CIB-S1P (transmembrane protease) interaction; (12) Mint2-S1P interaction; (13) PA1-P-glycerate DH interaction; (14) presenilin 1 (PS1)-Beta-ETF interaction; (15) PS1-GAPDH interaction; (16) CIB-adenosine triphosphate (ATP) synthase interaction; (17) KIAA0443-PI-4-kinase interaction; (18) KIAA0433-5HT-2A interaction; (19) KIAA0351-TRIO interaction; (20) Mint2-phosphodiesterase (PDE)-9A interaction; (21) BAX (Blc-2 family member)-slo K+ channel interaction; (22) focal adhesion kinase (FAK)2-sulfonylurea receptor (SUR)1 interaction; (23) CIB-SCD2 interaction; (24) rab11-FAK interaction; (25) FAK-Casein kinase II interaction; (26) GAK-GST trans. M3 interaction; (27) Bcr-PSD95 interaction; (28) Bcr-DLG3 interaction; (29) Bcr-Semaphorin F interaction; (30) Bcr-HTF4A interaction; and (31) Bcr-Snf2-related CREB-binding protein activator protein (SRCAP) interaction. Some acronyms not defined in specification.

BIOTECHNOLOGY - Preferred Protein Complex: The protein complex comprises CIB and **MLK**, a fragment of CIB and **MLK** or CIB and a fragment of **MLK**, or fragments of CIB and PDE-PA. Preferred Antibody: The antibody is preferably a monoclonal antibody.Preferred Method: Diagnosing a neurodegenerative disorder in an animal comprises assaying: (i) whether a protein complex as defined above is present in a tissue extract; (ii) for the ability of proteins to form a protein complex as defined above; and (iii) a mutation in a gene encoding a protein of a protein complex. The animal is a human. The diagnosis is for a predisposition to the neurodegenerative disorder or for the existence of the neurodegenerative disorder. The assay comprises a yeast two-hybrid assay, measuring in vitro a complex formed by combining the proteins of the protein complex, where the proteins are isolated from the animal, or mixing an antibody specific for the protein complex with a tissue extract from the animal and measuring the binding of the antibody. The complex is measured by binding with an antibody specific for the complex. The neurodegenerative disorder is Huntington's disease, **Parkinson**'s disease, dementia or Alzheimer's disease, particularly Alzheimer' s disease (AD). Determining whether a mutation in a gene encoding one of the proteins of the protein complex is useful for diagnosing a neurodegenerative disorder, comprises assaying for the ability of the protein with the mutation to form a complex with the other protein of the protein complex, where inability to form the complex indicates that the mutation is useful for diagnosing the existence or predisposition to a neurodegenerative disorder. The gene encoding one of the proteins can be an animal gene or a human gene. The assay employs a yeast two-hybrid assay, or involves measuring in vitro a complex formed by combining the proteins of the protein complex, where the proteins are isolated from an animal. The complex is measured by binding with an antibody specific for the complex. The neurodegenerative disorder is Huntington's disease, **Parkinson**'s disease, dementia or Alzheimer's disease. Screening for drug candidates capable of modulating the interaction of the proteins of a protein complex, comprises: (i) combining the proteins of the protein complex in the presence of a drug to form a first complex; (ii) combining the proteins in the absence of the drug to form a second complex; (iii) measuring the amount of the first complex and the second complex; and (iv) comparing the amount of the first complex with the amount of the second complex. If the amount of the first complex is greater than, or less than the amount of the second complex, then the drug is a drug candidate for modulating the interaction of the proteins of the protein complex. Screening is preferably in vitro screening. The complex is measured by binding with an antibody specific for the protein complexes. When the amount of the first complex is greater than the amount of the second complex, the drug is a candidate for promoting the interaction of the proteins, and when the amount of the first complex is less than the amount of the second complex, the drug is

a candidate for **inhibiting** the interaction of the proteins. Screening for drug candidates useful in treating a neurodegenerative disorder comprises: (i) measuring the activity of a protein selected from CIB and **MLK** in the presence of a drug; (ii) measuring the activity of the protein in the absence of the drug; and (iii) comparing the activity measured in steps (i) and (ii). If there is a difference in activity, the drug is a candidate for treating the neurodegenerative disorder. Selecting modulators of a protein complex formed between a first protein which is CIB or its homologue, derivative or fragment, and a second protein which is **MLK**, or its homologue, derivative or fragment, comprises providing a protein complex, contacting the protein complex with a test compound, and determining the presence or absence of binding of the test compound to the protein complex. Selecting modulators of an interaction between a first protein and a second protein, where the first protein is CIB or its homologue, derivative or fragment, and the second protein is **MLK** or its homologue, derivative or fragment, comprises contacting the first protein with the second protein in the presence of a test compound, and determining the interaction between the first protein and the second protein. At least the first or the second protein is a fusion protein having a detectable tag. The interaction between the first and second protein is determined in a substantially cell free environment or in a host cell such as a yeast cell. The test compound is provided in a phage display library or a combinatorial library. Selecting modulators of a protein complex formed from a first protein which is CIB or its homologue, derivative or fragment, and a second protein which is **MLK** or its homologue, derivative or fragment, comprises contacting the protein complex with a test compound, and determining the interaction between the first protein and the second protein. The method may also comprise providing in a host cell a first fusion protein having the first polypeptide, and a second fusion protein having the second polypeptide, where a DNA binding domain is fused to one of the first and second polypeptides while a transcription-activating domain is fused to the other of the first and second polypeptides; providing in the host cell a reporter gene, where the transcription of the reporter gene is determined by the interaction between the first polypeptide and the second polypeptide; allowing the first and second fusion proteins to interact with each other within the host cell in the presence of a test compound; and determining the presence or absence of expression of the reporter gene. The host cell is a yeast cell. Alternatively, the method comprises providing atomic coordinates defining a 3-dimensional structure of a protein complex formed by the first polypeptide and the second polypeptide; and designing or selecting compounds capable of modulating the interaction between a first polypeptide and a second polypeptide based on the atomic coordinates. Selecting modulators of **MLK** comprises contacting **MLK** with a test compound, and determining binding of the test compound to **MLK**. The test compound is provided in a phage display library or in a combinatorial library. Identifying a compound that binds to **MLK** in vitro comprises contacting a test compound with **MLK** for a time allowing the formation of a complex and detecting for the formation of a complex by detecting **MLK** or the compound in the complex, and if a complex is detected, a compound that binds to **MLK** is consequently identified. The method for providing **inhibitors** of an interaction between a first polypeptide and a second polypeptide, where the first polypeptide is CIB or its homologue, derivative or fragment, and the second polypeptide is **MLK** or its homologue, derivative or fragment, comprises providing atomic coordinates defining a three-dimensional structure of a protein complex formed by the first polypeptide and the second polypeptide; and designing or selecting compounds capable of interfering with the interaction between the first polypeptide and a second polypeptide based on the atomic coordinates. Modulating a protein complex having a first protein which is CIB interacting with a second protein which is PDE-gA, in a cell, comprises administering to the cell a compound capable of modulating the protein complex. The compound is selected a compound

capable of interfering with the interaction between the first protein and the second protein, a compound capable of binding a first protein and the second protein, a compound comprising a peptide having a contiguous span of amino acids of at least 4 amino acids of the second protein and capable of binding the first protein, a compound comprising a peptide capable of binding the first protein and having an amino acid sequence of 4-30 amino acids that is at least 75% identical to a contiguous span of amino acids of the second protein of the same length, a compound comprising a peptide having a contiguous span of amino acids of at least 4 amino acids of first protein and capable of binding the second protein, a compound comprising a peptide capable of binding second protein and having an amino acid sequence of 4-30 amino acids that is at least 75% identical to a contiguous span of amino acids of first protein of the same length, a compound which is an antibody immunoreactive with the first protein or the second protein, a compound which is a nucleic acid encoding an antibody immunoreactive with the first protein or the second protein, a compound which modulates the expression of the first protein or the second protein, and compound which is an antisense compound or a ribozyme specifically hybridizing to a nucleic acid encoding the first protein or the second protein, or its complement. The nucleic acid encodes the first protein or the second protein. Modulating a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**, in a cell, comprises administering to the cell a peptide capable of interfering with the interaction between the first protein and the second protein, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. The peptide is covalently linked to the transporter selected from penetratins, l-Tat49-57, d-Tat49-57, retro-inverso isomers of l- or d-Tat49-57, L-arginine oligomers, D- arginine oligomers, L-lysine oligomers, D-lysine oligomers, L-histine oligomers, D-histine oligomers, L-ornithine oligomers, D-ornithine oligomers, short peptide sequences derived from fibroblast growth factor, Galparan, and HSV-1 structural protein VP22, and their peptoid analogs. Modulating the interaction of **MLK** with a ligand in a cell comprises administering to the cell a compound capable of modulating the interaction. The ligand is preferably CIB, and the compound is selected from: a compound which interferes with the interaction; a compound which binds to **MLK** or the ligand; a compound which comprises a peptide having a contiguous span of at least 4 amino acids of **MLK** and capable of binding the ligand; a compound which comprises a peptide capable of binding the ligand and having an amino acid sequence of 4-30 amino acids that is at least 75% identical to a contiguous span of amino acids of **MLK** of the same length; a compound which is an antibody immunoreactive with **MLK** or the ligand; a compound which is a nucleic acid encoding an antibody immunoreactive with the ligand or **MLK**; a compound which modulates the expression of **MLK** or the ligand; a compound which is an antisense compound or a ribozyme specifically hybridizing to a nucleic acid encoding the ligand or its complement; and a compound which is an antisense compound or a ribozyme specifically hybridizing to a nucleic acid encoding **MLK** or its complement. Modulating neuronal death in a patient having a neurodegenerative disorder comprises modulating a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**, or administering to the patient a compound capable of modulating a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**. The method may also comprise administering to the cell a peptide capable of interfering with the interaction between a first protein which is CIB and a second protein which is **MLK**, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. Treating a neurodegenerative disorder comprises administering to a patient: (i) a compound capable of modulating a protein complex having a first protein which is CIB interacting with a second protein which is **MLK**;(ii) or a peptide capable of interfering with the interaction between the first protein and the second protein, where the peptide is

associated with a transporter capable of increasing cellular uptake of the peptide; or (iii) a compound capable of modulating the activity of **MLK**. Modulating **MLK** activities of a protein in a cell comprises administering to the cell a peptide having a contiguous span of at least 4 amino acids of CIB capable of binding **MLK**, where the peptide is associated with a transporter capable of increasing cellular uptake of the peptide. Preferred Animal Model: In the non-human animal model for a neurodegenerative disorder, the formation of the protein complex has been altered as a result of: (i) over-expression of at least one of the proteins of the protein complex; (ii) replacement of a gene for at least one of the proteins of the protein complex with a gene from a second animal and expression of the protein; (iii) expression of a mutant form of at least one of the proteins of the protein complex; (iv) a lack of expression of at least one of the proteins of the protein complex; or (v) reduced expression of at least one of the proteins of the protein complex. The biological activity of the non-human animal model has been altered as a result of a disruption in the formation of the complex or in the action of the complex. Formation of the complex is disrupted by binding an antibody or a small molecule to at least one of the proteins which form the protein complex. The action of the complex is disrupted by binding a small molecule or an antibody to the complex. Preferred Host Cell: The host cell is a yeast cell, and the first and second proteins are expressed in fusion proteins. One of the first and second nucleic acids is linked to a nucleic acid encoding a DNA binding domain, and the other of the first and second nucleic acids is linked to a nucleic acid encoding a transcription-activation domain, where two fusion proteins can be produced in the host cell. The host cell further comprises a reporter gene, where expression of the reporter gene is determined by the interaction between the first protein and the second protein.

ACTIVITY - Neuroprotective; Nootropic; Antiparkinsonian; Anticonvulsant.

MECHANISM OF ACTION - CIB-**mixed lineage kinase** 2 protein complex modulator. No supporting data is given in the source material.

USE - The AD interacting proteins are useful as new targets for the identification of useful pharmaceuticals, new targets for diagnostic tools in the identification of individuals at risk, sequences for producing transformed cell lines, cellular models and animal models, and new bases for therapeutic intervention in neurodegenerative disorders, particularly AD. The proteins and DNA encoding the proteins may also be used in the development of diagnostic and therapeutic tools against AD. Modulators of the protein complex are useful for treating a neurodegenerative disorder including Huntington's disease, **Parkinson**'s disease, dementia or Alzheimer's disease.

EXAMPLE - None given in the source material. (91 pages)

L3 ANSWER 33 OF 36 CIN COPYRIGHT 2003 ACS
AN 31(34):33284P CIN
TI Clinical status
SO BioCentury, 5 Aug 2002 (20020805), 10(34, Pt. 2), p. B13. ISSN: 1097-7201; CODEN: BICEFS.
LA English
AB CEP-1347 from Cephalon Inc. (CEPH), West Chester, Penn., and H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark, is a **mixed lineage kinase** (**MLK**) **inhibitor** of c- Jun N-terminal kinase (JNK) activation used to treat **Parkinson**'s disease. CEPH and LUN began a North American Phase II/III trial of CEP-1347 in 800 patients with early stage **Parkinson**'s disease (PD). The double-blind, placebo-controlled, dose-finding trial will assess whether CEP-1347 can delay disability due to PD progression during 2 years of treatment. LUN has exclusive commercial rights to CEP-147 in Europe and certain other areas. CEPH retains U.S. rights, and Kyowa Hakko Kogyo Co. Ltd. (Tokyo, Japan) has exclusive rights in the rest of the world.

L3 ANSWER 34 OF 36 PHARMAML COPYRIGHT 2003 MARKETLETTER
AN 1664756 PHARMAML
TI Lundbeck, Cephalon to trial **Parkinson**'s drug
SO Marketletter August 12, 2002
DT Newsletter
WC 95
TX H Lundbeck of Denmark and the USA's Cephalon have started clinical trials of CEP-1347, an **inhibitor** of members of the **mixed lineage kinase** (**MLK**) family, in patients with early-stage **Parkinson**'s disease. The objective of the study, which is the largest ever undertaken by Lundbeck and will enroll upwards of 800 patients in the USA and Canada, is to determine whether CEP-1347 may be effective in delaying disability due to progression of PD over a two-year period. The two firms note that recent experiments suggest that CEP-1347 can **inhibit** apoptosis (programmed cell death) in dopaminergic neurons.

L3 ANSWER 35 OF 36 PHIN COPYRIGHT 2003 PJB

AN 2002:15184 PHIN
DN S00765818
DED 7 Aug 2002
TI Novel **Parkinson**'s drug in Phase II/III
SO Scrip (2002) No. 2770 p21
DT Newsletter
FS FULL

L3 ANSWER 36 OF 36 PROMT COPYRIGHT 2003 Gale Group

AN 2002:401466 PROMT
TI Lundbeck, Cephalon to trial **Parkinson**'s drug.
SO Marketletter, (12 Aug 2002) .
ISSN: ISSN: 0951-3175.
PB Marketletter Publications Ltd.
DT Newsletter
LA English
WC 95
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB H Lundbeck of Denmark and the USA's Cephalon have started clinical trials of CEP-1347, an **inhibitor** of members of the **mixed lineage kinase** (**MLK**) family, in patients with early-stage **Parkinson**'s disease. The objective of the study, which is the largest ever undertaken by Lundbeck and will enroll upwards of 800 patients in the USA and Canada, is to determine whether CEP-1347 may be effective in delaying disability due to progression of PD over a two-year period. The two firms note that recent experiments suggest that CEP-1347 can **inhibit** apoptosis (programmed cell death) in dopaminergic neurons.

Subscription: 499.00 British pounds per year. Published weekly. 54-55 Wilton Road, London SW1V 1DE., United Kingdom

=> d cbib 1-21

L3 ANSWER 1 OF 36 USPATFULL DUPLICATE 1
2002:246742 Heterocyclic substituted pyrazolones.
Singh, Jasbir, Gilbertsville, PA, United States
Tripathy, Rabindranath, Landenberg, PA, United States
Cephalon, Inc., West Chester, PA, United States (U.S. corporation)
US 6455525 B1 20020924
APPLICATION: US 2000-702191 20001031 (9)
PRIORITY: US 1999-163377P 19991104 (60)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 2 OF 36 USPATFULL
2003:11179 4-Pyrimidinamine derivatives, pharmaceutical compositions and related methods.
Grant, Elfrida R., Perrineville, NJ, UNITED STATES
Brown, Frank K., Whitehouse Station, NJ, UNITED STATES
Zivin, Robert Allan, Skillman, NJ, UNITED STATES
McMillan, Michael, Somerville, NJ, UNITED STATES
Zhong, Zhong, Bridgewater, NJ, UNITED STATES
Scott, Malcolm, Telford, PA, UNITED STATES
Reitz, Allen B., Lansdale, PA, UNITED STATES
Ross, Tina Morgan, Audubon, PA, UNITED STATES
US 2003008883 A1 20030109
APPLICATION: US 2001-922874 A1 20010806 (9)
PRIORITY: US 2000-223791P 20000808 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 3 OF 36 USPATFULL
2002:344488 2-pyridinamine compositions and related methods.
Grant, Elfrida R. Flemington, NJ, UNITED STATES
Brown, Frank K., Whitehouse Station, NJ, UNITED STATES
Zivin, Robert Allan, Skillman, NJ, UNITED STATES
McMillan, Michael, Somerville, NJ, UNITED STATES
Zhong, Zhong, Bridgewater, NJ, UNITED STATES
Benjamin, Daniel, Barnegat, NJ, UNITED STATES
US 2002198219 A1 20021226
APPLICATION: US 2001-922658 A1 20010806 (9)
PRIORITY: US 2000-223795P 20000808 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 36 USPATFULL
2002:343940 HUMAN CHORDIN-RELATED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM.
JACOBS, KENNETH, NEWTON, MA, UNITED STATES
MCCOY, JOHN M., READING, MA, UNITED STATES
LAVALLIE, EDWARD R., HARVARD, MA, UNITED STATES
COLLINS RACIE, LISA A., ACTON, MA, UNITED STATES
MERBERG, DAVID, ACTON, MA, UNITED STATES
TREACY, MAURICE, DUBLIN, IRELAND
DIBLASIO-SMITH, ELIZABETH, TYNGSBORO, MA, UNITED STATES
WIDOM, ANGELA, ACTON, MA, UNITED STATES
US 2002197666 A1 20021226
APPLICATION: US 1999-373967 A1 19990813 (9)
PRIORITY: US 1998-95880P 19980810 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 36 USPATFULL
2002:294612 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT (U.S. corporation)
US 2002164655 A1 20021107
APPLICATION: US 2001-973941 A1 20011011 (9)
PRIORITY: US 2000-240790P 20001017 (60)
US 2001-304775P 20010713 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 36 USPATFULL
2002:229107 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Marc, Salt Lake City, UT, UNITED STATES

Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
US 2002124273 A1 20020905
APPLICATION: US 2001-973965 A1 20011011 (9)
PRIORITY: US 2000-240790P 20001017 (60)
US 2001-304775P 20010713 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 36 USPATFULL
2002:221785 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT (U.S. corporation)
US 2002119927 A1 20020829
APPLICATION: US 2001-972757 A1 20011009 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 8 OF 36 USPATFULL
2002:221020 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT, UNITED STATES (U.S. corporation)
US 2002119155 A1 20020829
APPLICATION: US 2001-972038 A1 20011009 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 9 OF 36 USPATFULL
2002:214220 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT, UNITED STATES (U.S. corporation)
US 2002115607 A1 20020822
APPLICATION: US 2001-975072 A1 20011012 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 10 OF 36 USPATFULL
2002:214219 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT (U.S. corporation)
US 2002115606 A1 20020822
APPLICATION: US 2001-973964 A1 20011011 (9)
PRIORITY: US 2000-240790P 20001017 (60)
US 2001-304775P 20010713 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 11 OF 36 USPATFULL
2002:213743 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean-Mark, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc. (U.S. corporation)
US 2002115119 A1 20020822

APPLICATION: US 2001-973063 A1 20011010 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 12 OF 36 USPATFULL
2002:113426 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT, UNITED STATES (U.S. corporation)
US 2002114799 A1 20020822
APPLICATION: US 2001-973077 A1 20011010 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 13 OF 36 USPATFULL
2002:198673 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT, UNITED STATES (U.S. corporation)
US 2002106773 A1 20020808
APPLICATION: US 2001-973064 A1 20011010 (9)
PRIORITY: US 2000-240790P 20001017 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 14 OF 36 USPATFULL
2002:198576 Protein-protein interactions in neurodegenerative diseases.
Roch, Jean Marc, Salt Lake City, UT, UNITED STATES
Bartel, Paul L., Salt Lake City, UT, UNITED STATES
Heichman, Karen, Salt Lake City, UT, UNITED STATES
Myriad Genetics, Inc., Salt Lake City, UT (U.S. corporation)
US 2002106676 A1 20020808
APPLICATION: US 2001-973963 A1 20011011 (9)
PRIORITY: US 2000-240790P 20001017 (60)
US 2001-304775P 20010713 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 15 OF 36 USPATFULL
2002:192157 Indazole derivatives as JNK inhibitors and compositions and methods related thereto.
Bhagwat, Shripad S., San Diego, CA, UNITED STATES
Satoh, Yoshitaka, San Diego, CA, UNITED STATES
Sakata, Steven T., San Diego, CA, UNITED STATES
Buhr, Chris A., Redwood City, CA, UNITED STATES
Albers, Ronald, La Jolla, CA, UNITED STATES
Sapienza, John, Chula Vista, CA, UNITED STATES
Plantevin, Veronique, San Diego, CA, UNITED STATES
Chao, Qi, San Diego, CA, UNITED STATES
Sahasrabudhe, Kiran, San Diego, CA, UNITED STATES
Ferri, Rachel, San Diego, CA, UNITED STATES
US 2002103229 A1 20020801
APPLICATION: US 2001-910950 A1 20010723 (9)
PRIORITY: US 2000-221799P 20000731 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 16 OF 36 USPATFULL
2002:119931 Selected fused pyrrolocarbazoles.
Gingrich, Diane E., Downingtown, PA, UNITED STATES
Hudkins, Robert L., Chester Springs, PA, UNITED STATES

US 2002061920 A1 20020523
APPLICATION: US 2001-935285 A1 20010822 (9)
PRIORITY: US 2000-227803P 20000825 (60)
US 2001-278455P 20010323 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 17 OF 36 USPATFULL
2002:112612 JNK inhibitors for the treatment of neurological disorders.
Liu, Ya Fang, Boston, MA, UNITED STATES
US 2002058245 A1 20020516
APPLICATION: US 2002-42614 A1 20020109 (10)
PRIORITY: US 1998-85439P 19980514 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 18 OF 36 USPATFULL
2002:92229 Model for alzheimer's disease and other neurodegenerative diseases.
Lynch, Gary, Irvine, CA, UNITED STATES
Bi, Xiaoning, Irvine, CA, UNITED STATES
US 2002048746 A1 20020425
APPLICATION: US 2001-917789 A1 20010731 (9)
PRIORITY: US 2001-283352P 20010413 (60)
US 2000-222060P 20000731 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 19 OF 36 USPATFULL
2002:48623 Novel multicyclic compounds and the use thereof.
Ator, Mark A., Paoli, PA, UNITED STATES
Bihovsky, Ron, Wynnewood, PA, UNITED STATES
Chatterjee, Sankar, Wynnewood, PA, UNITED STATES
Dunn, Derek, Thorndale, PA, UNITED STATES
Hudkins, Robert L., Chester Springs, PA, UNITED STATES
US 2002028815 A1 20020307
APPLICATION: US 2001-850858 A1 20010508 (9)
PRIORITY: US 2000-202947P 20000509 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 20 OF 36 USPATFULL
2002:12228 **MLK inhibitors** for the treatment of neurological disorders.
Liu, Ya Fang, Boston, MA, UNITED STATES
US 2002006606 A1 20020117
APPLICATION: US 2001-886964 A1 20010621 (9)
PRIORITY: US 1998-85439P 19980514 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

Mine

L3 ANSWER 21 OF 36 USPATFULL
2000:57542 Post-mitotic neurons containing adenovirus vectors that modulate apoptosis and growth.
Miller, Freda D., Montreal, Canada
Slack, Ruth S., Napean, Canada
McGill University, West Montreal, Canada (non-U.S. corporation)
US 6060247 20000509
APPLICATION: US 1997-995050 19971118 (8)
PRIORITY: US 1996-31057P 19961118 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d all 31

L3 ANSWER 31 OF 36 ADISINSIGHT COPYRIGHT 2003 (ADIS)
AN 1998:4258 ADISINSIGHT
SO Adis R&D Insight
DN 004793
CDAT Dec 12, 2002
CN CEP 1347
CN KT 7515
CN 9alpha,12alpha-Epoxy-5,16-bis(ethylsulfanylmethyl)-10beta-hydroxy-9-methyl-1-oxo-2,3,9,10,11,12alpha-hexahydro-1H-diindolo(1,2,3-fg:3',2,1-kl)pyrrolo(3,4-i)1,6)benzodiazocine-10-carboxylic acid methyl ester
MF C33 H33 N3 O5 S2
STR
STRUCTURE DIAGRAM IS NOT AVAILABLE
CC EPHMRA ATC CODE: **N4A Anti-Parkinson Drugs**
CC WHO ATC CODE: **N04 Anti-Parkinson Drugs**
HDP Phase II
DSTA Phase II, Canada, **Parkinson**'s disease
Phase II, European Union, **Parkinson**'s disease
Phase II, United States, **Parkinson**'s disease
ORIGINATOR: Kyowa Hakko (Japan)
PARENT: Kyowa Hakko
LICENSEE: Cephalon; Lundbeck A/S
WC 323

TX TEXT
Introduction:
CEP 1347 (KT 7515), a **mixed lineage kinase inhibitor**, is an orally active analogue of K 252A licensed by Cephalon from Kyowa Hakko. The neuronal survival properties of CEP 1347 may relate to its ability to **inhibit** the activation of c-jun N-terminal kinase, a key kinase in some forms of stress-induced neuronal death and perhaps apoptosis. Two pilot phase IIa studies have been completed. In August 2002, Cephalon and Lundbeck announced the initiation of a large phase II/III study involving approximately 800 patients with **Parkinson**'s disease recruited from up to 65 locations in the US and Canada. The placebo-controlled, randomised, double-blind study will assess the efficacy of CEP 1347 in delaying disability due to the progression of **Parkinson**'s disease over a 2-year period. CEP 1347 may also have potential in Alzheimer's disease.

Cephalon was granted exclusive marketing rights in the US to the K 252A series from Kyowa Hakko. Lundbeck has acquired European marketing rights to CEP 1347 from Cephalon. Lundbeck is co-financing development of CEP 1347 for **Parkinson**'s disease.

TX EVALUATION:
Parkinson's disease 52 (Unknown route).

TX COMMERCIAL SUMMARY:
Parkinson's / Kinase inhibitor

Company	Region	Launch Date	Peak Sales	Patent Expiry
Lundbeck	Eur	2007	$150m	

TX PHARMACOLOGY OVERVIEW:
Pharmacodynamics:
Neuroprotective activity in rodent and primate models of **Parkinson**'s disease
Mechanism of action:
Mixed-lineage kinase inhibitors
Protein kinase **inhibitors**
Kinase **inhibitors**

Enzyme **inhibitors**

TX CLINICAL OVERVIEW:
Route(s) of Administration: PO
Drug Interactions:
Unknown.

TX PHARMACOLOGY:
Pharmacodynamics (**Parkinson**'s Disease and Movement Disorders):
Preclinical studies: CEP 1347 prevented MPTP-mediated nigrostriatal dopaminergic degeneration in mice. In a high dose MPTP model where there was a 80% loss of striatal dopaminergic terminals and substantia nigra dopaminergic neurons, CEP 1347 (0.3 mg/kg/day beginning 4h before administration of MPTP) significantly reduced these losses to 30% and 50%, respectively. The neuroprotective effects of CEP 1347 were not evident when it was administered after maximal loss of dopaminergic neurons (7 days after MPTP administration)/1/.
In a primate model of **Parkinson**'s disease, vehicle-treated animals developed symptoms in 4.2 weeks, while 75% of animals treated with CEP 1347 remained symptom-free over the 10-week treatment period and the remaining 25% developed symptoms by 7.5 weeks. As well as the CEP 1347-associated delay in onset of symptoms, cell counts in the substantia nigra revealed that dopaminergic nerve cell numbers were significantly higher in animals treated with CEP 1347/2/.

RDAT	RNTE
08 Aug 2002	**Phase-II/III clinical trials in Parkinson's disease in USA (PO)**
04 Dec 2001	Sales forecasts reviewed by Lehman Brothers
19 Nov 2001	**Phase-II clinical trials for Parkinson's disease in European Union (PO)**
19 Nov 2001	**Phase-II clinical trials for Parkinson's disease in USA (PO)**
21 May 2001	**Phase-I clinical trials for Parkinson's disease in European Union (PO)**
18 Jan 2001	Phase-I clinical trials for Neuroprotection in USA (PO)
18 Jan 2001	Profile reviewed by Lundbeck
04 Nov 1999	**Data have been added to the Parkinson's Disease and Movement Disorders pharmacodynamics section (801106)**
01 Sep 1999	**Phase-I clinical trials for Parkinson's disease in USA (PO)**
24 Jun 1999	Lundbeck has acquired European rights to CEP 1347
02 Mar 1999	Preclinical development for Neuroprotection in USA (Unknown route)
08 Mar 1995	New profile
08 Mar 1995	Preclinical development for Neuroprotection in USA (Unknown route)

RE 1. Saporito MS, Brown EM, et al. CEP-1347/KT-7515, an inhibitor of c-jun N-terminal kinase activation, attenuates the 1-methyl-4-phenyl tetrahydropyridine-mediated loss of nigrostriatal dopaminergic neurons in vivo. Journal of Pharmacology and Experimental Therapeutics. 288: 421-427, Feb 1999. (English).
2. Cephalon Inc. New compound, CEP-1347, demonstrates potential for halting the progression of Parkinson's disease. Media Release. : (2 pages), 27 Oct 1999. Available from: URL: http://www.cephalon.com. (English).

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	124.62	128.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL

	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.95	-1.95

STN INTERNATIONAL LOGOFF AT 10:57:44 ON 07 FEB 2003

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 * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * *


FILE 'HOME' ENTERED AT 12:20:46 ON 07 FEB 2003

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,
       BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
       CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE,
       DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 12:20:57 ON 07 FEB 2003

64 FILES IN THE FILE LIST IN STNINDEX

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search error messages that display as 0* with SET DETAIL OFF.


=> s (((mulitple or mixed)(w) lineage(w) kinase) or mlk) and inhib? and py<1998
           0*  FILE ADISINSIGHT
   6 FILES SEARCHED...
           7   FILE BIOSIS
   9 FILES SEARCHED...
           5   FILE BIOTECHNO
           2   FILE CABA
           2   FILE CANCERLIT
  14 FILES SEARCHED...
           9   FILE CAPLUS
  18 FILES SEARCHED...
           0*  FILE CONFSCI
           3   FILE CROPU
           1   FILE DDFU
          13   FILE DGENE
           3   FILE DRUGU
           5   FILE EMBASE
  32 FILES SEARCHED...
           6   FILE ESBIOBASE
           0*  FILE FEDRIP
           0*  FILE FOREGE
  42 FILES SEARCHED...
           3   FILE LIFESCI
           0*  FILE MEDICONF
           5   FILE MEDLINE
  47 FILES SEARCHED...
           2   FILE PASCAL
  50 FILES SEARCHED...
           0*  FILE PHAR
           6   FILE SCISEARCH
  56 FILES SEARCHED...
           2   FILE TOXCENTER
           4   FILE USPATFULL
           1   FILE WPIDS
  63 FILES SEARCHED...
           1   FILE WPINDEX

  19 FILES HAVE ONE OR MORE ANSWERS,   64 FILES SEARCHED IN STNINDEX

L1   QUE (((MULITPLE OR MIXED)(W) LINEAGE(W) KINASE) OR MLK) AND INHIB? AND PY<
       1998
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=> d rank
F1          13   DGENE
F2           9   CAPLUS
F3           7   BIOSIS
F4           6   ESBIOBASE
F5           6   SCISEARCH
F6           5   BIOTECHNO
F7           5   EMBASE
F8           5   MEDLINE
F9           4   USPATFULL
F10          3   CROPU
F11          3   DRUGU
F12          3   LIFESCI
F13          2   CABA
F14          2   CANCERLIT
F15          2   PASCAL
F16          2   TOXCENTER
F17          1   DDFU
F18          1   WPIDS
F19          1   WPINDEX


=> file f2-8 f10 f12-18
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                            6.60       6.81

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2 FILES SEARCHED...
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L2 58 L1

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PROCESSING COMPLETED FOR L2
L3 17 DUP REM L2 (41 DUPLICATES REMOVED)
ANSWERS '1-9' FROM FILE CAPLUS
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ANSWER '11' FROM FILE ESBIOBASE
ANSWER '12' FROM FILE SCISEARCH
ANSWERS '13-14' FROM FILE CROPU
ANSWER '15' FROM FILE CABA
ANSWER '16' FROM FILE CANCERLIT
ANSWER '17' FROM FILE PASCAL

=> d bib abs 1-17

L3 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
AN 1997:595184 CAPLUS
DN 127:273200
TI Activation of the hematopoietic progenitor kinase-1 (HPK1)-dependent, stress-activated c-Jun N-terminal kinase (JNK) pathway by transforming growth factor .beta. (TGF-.beta.)-activated kinase (TAK1), a kinase mediator of TGF .beta. signal transduction
AU Wang, Wenfu; Zhou, Guisheng; Hu, Mickey C.-T.; Yao, Zhengbin; Tan, Tse-Hua
CS Department Microbiology Immunology, Baylor College Medicine, Houston, TX, 77030, USA
SO Journal of Biological Chemistry (**1997**), 272(36), 22771-22775
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Transforming growth factor .beta. (TGF-.beta.)-activated kinase (TAK1) is known for its involvement in TGF-.beta. signaling and its ability to activate the p38-mitogen-activated protein kinase (MAPK) pathway. This report shows that TAK1 is also a strong activator of c-Jun N-terminal kinase (JNK). Both the wild-type and a constitutively active mutant of TAK1 stimulated JNK in transient transfection assays. Mitogen-activated protein kinase kinase 4 (MKK4)/stress-activated protein kinase/extracellular signal-regulated kinase (SEK1), a dual-specificity kinase that phosphorylates and activates JNK, synergized with TAK1 in activating JNK. Conversely, a dominant-neg. MKK4/SEK1 mutant **inhibited** TAK1-induced JNK activation. A kinase-defective mutant of TAK1 effectively suppressed hematopoietic progenitor kinase-1 (HPK1)-induced JNK activity but had little effect on germinal center kinase activation of JNK. There are two addnl. MAPK kinase kinases, MEKK1 and **mixed lineage kinase** 3 (MLK3), that are also downstream of HPK1 and upstream of MKK4/SEK mutant. However, because

the dominant-neg. mutants of MEKK1 and MLK3 did not **inhibit** TAK1-induced JNK activity, the authors conclude that activation of JNK1 by TAK1 is independent of MEKK1 and MLK3. In addn. to TAK1, TGF-.beta. also stimulated JNK activity. Taken together,these results identify TAK1 as a regulator in the HPK1 .fwdarw. TAK1 .fwdarw. MKK4/SEK1 .fwdarw. JNK kinase cascade and indicate the involvement of JNK in the TGF-.beta. signaling pathway. The authors' results also suggest the potential roles of TAK1 not only in the TGF-.beta. pathway but also in the other HPK1/JNK1-mediated pathways.

L3 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
AN 1997:440776 CAPLUS
DN 127:160108
TI Decreased potassium stimulates bone resorption
AU Bushinsky, David A.; Riordon, Daniel R.; Chan, Jeannie S.; Krieger, Nancy S.
CS Nephrology Unit, Department Medicine, University Rochester School Medicine, Rochester, NY, 14642, USA
SO American Journal of Physiology (**1997**), 272(6, Pt. 2), F774-F780
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB Metabolic acidosis induces net calcium efflux (JCa) from cultured bone, in part, through an increase in osteoclastic resorption and a decrease in osteoblastic formation. In humans provision of base as potassium (K+) citrate, but not sodium (Na+) citrate, reduces urine Ca (UCa), and oral KHCO3 decreases bone resorption and UCa in postmenopausal women. Potassium deprivation alone leads to an increase in UCa. To det. whether decreased extracellular K+ concn. ([K+]) at a const. pH, PCO2, and [HCO3-] alters JCa and bone cell activity, we measured JCa, osteoblastic collagen synthesis, and osteoclastic .beta.-glucuronidase release from neonatal mouse calvariae cultured for 48 h in medium of varying [K+]. Calvariae were cultured in control medium (.apprxeq.4 mM [K+]) or medium with mildly low K+ (**MLK**, .apprxeq.3 mM [K+]), very low K+ (VLK, .apprxeq.2 mM [K+]), or extremely low K+ (ELK, .apprxeq.1 mM [K+]) (n .gtoreq. 9 in each group). Compared with control, ELK, but not **MLK** or VLK, resulted in a marked increase in JCa and an increase in .beta.-glucuronidase release and a decrease in collagen synthesis. JCa was correlated directly with medium .beta.-glucuronidase activity and inversely with collagen synthesis. To det. whether the redn. in medium [K+] was assocd. with a decrease in intracellular pH (pHi), we measured pHi in MC3T3-E1 cells, a mouse osteoblastic cell line. Incubation in 1 mM [K+] led to a significant decrease in pHi compared with 3 mM [K+]. Thus incubation in a reduced [K+] medium stimulates JCa and osteoclastic enzyme release and **inhibits** osteoblastic collagen synthesis, which may be mediated by a redn. in bone cell pH.

L3 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
AN 1997:143115 CAPLUS
DN 126:236375
TI MEKKs, GCKs, **MLKs**, PAKs, TAKs, and Tpls: upstream regulators of the c-Jun amino-terminal kinases?
AU Fanger, Gary R.; Gerwins, Par; Widmann, Christian; Jarpe, Matthew B.; Johnson, Gary L.
CS Division of Basic Sciences, Program in Molecular Signal Transduction, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, 80206, USA
SO Current Opinion in Genetics & Development (**1997**), 7(1), 67-74
CODEN: COGDET; ISSN: 0959-437X
PB Current Biology
DT Journal; General Review
LA English
AB A discussion and review with 58 refs. Regulation of the mitogen-activated protein kinase (MAPK) family members, which include the extracellular

response kinases (ERKs), p38/HOG1, and the c-Jun amino-terminal kinases (JNKs), plays a central role in mediating the effects of diverse stimuli encompassing cytokines, hormones, growth factors and stresses such as osmotic imbalance, heat shock, **inhibition** of protein synthesis and irradn. A rapidly increasing no. of kinases that activate the JNK pathways has been described recently, including the MAPK/ERK kinase kinases, p21-activated kinases, germinal center kinase, **mixed lineage kinases**, tumor progression locus 2, and TGF-.beta.-activated kinase. Thus, regulation of the JNK pathway provides an interesting example of how many different stimuli can converge into regulating pathways crit. for the detn. of cell fate.

L3 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
AN 1996:259755 CAPLUS
DN 124:281127
TI Muscle localized receptor tyrosine kinase cDNA sequence of mouse, recombinant production, and therapeutic uses
IN Wood, Clive; Caruso, Anthony
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9602644	A1	19960201	WO 1995-US8493	19950706 <--
	W: AU, CA, JP, MX				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9529633	A1	19960216	AU 1995-29633	19950706 <--
PRAI	US 1994-277803		19940720		
	US 1995-384710		19950201		
	WO 1995-US8493		19950706		

AB Polynucleotides encoding novel receptor tyrosine kinases designated '**mlk**' are disclosed. **Mlk** proteins and methods for their prodn., ligands for the **mlk** receptor and methods for their identification, and **inhibitors** of binding of **mlk** and its ligands and methods for their identification are also disclosed.

L3 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 5
AN 1996:498405 CAPLUS
DN 125:136222
TI The **mixed lineage kinase** SPRK phosphorylates and activates the stress-activated protein kinase activator, SEK-1
AU Rana, Ajay; Gallo, Kathleen; Godowski, Paul; Hirai, Shu-ichi; Ohno, Shigeo; Zon, Leonard; Kyriakis, John M.; Avruch, Joseph
CS Diabetes Unit and Med. Service, Massachusetts Gen. Hosp., Boston, MA, 02129, USA
SO Journal of Biological Chemistry (**1996**), 271(32), 19025-19028
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB SPRK (also called PTK-1 and **MLK**-3), a member of the **mixed lineage kinase** subfamily of (Ser/Thr) protein kinases, encodes an amino-terminal SH3 domain followed by a kinase catalytic domain, two leucine zippers interrupted by a short spacer, a Rac/Cdc42 binding domain, and a long carboxyl-terminal proline-rich region. We report herein that SPRK activates the stress-activated protein kinases (SAPKs) but not ERK-1 during transient expression in COS cells; the p38 kinase is activated modestly (1.3-2 fold) but consistently. SPRK also activates cotransfected SEK-1/MKK-4, a dual specificity kinase which phosphorylates and activates SAPK. Reciprocally, expression of mutant, inactive SEK-1 **inhibits** completely the basal and SPRK-activated SAPK activity. Immunopptd. recombinant SPRK is able to phosphorylate and

activate recombinant SEK-1 in vitro to an extent comparable to that achieved by MEK kinase-1. These results identify SPRK as a candidate upstream activator of the stress-activated protein kinases, acting through the phosphorylation and activation of SEK-1.

L3 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
AN 1996:424041 CAPLUS
DN 125:111143
TI Characterization of dual leucine zipper-bearing kinase, a **mixed lineage kinase** present in synaptic terminals whose phosphorylation state is regulated by membrane depolarization via calcineurin
AU Mata, Marina; Merritt, Steven E.; Fan, Guang; Yu, Geng Geng; Holzman, Lawrence B.
CS Dep. Neurology, Univ. Pittsburgh Medical School, Pittsburgh, PA, 15261, USA
SO Journal of Biological Chemistry (**1996**), 271(28), 16888-16896
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The biochem. and regulation of dual leucine zipper bearing kinase (DLK), a member of the **mixed lineage kinase** or **MLK** subfamily of protein kinases, was examd. in the nervous system. DLK transcript expression in the nervous system was predominantly neuronal. DLK protein was present in synaptic terminals where it was assocd. with both plasma membrane and cytosol fractions. Within these two fractions, DLK had differing characteristics. Cytosolic DLK existed in both a phosphorylated and dephosphorylated state; DLK assocd. with plasma membrane existed in the dephosphorylated state only. On nonreducing SDS-PAGE, cytosolic DLK migrated at 130 kDa, while membrane assocd. DLK migrated with an apparent Mr .gtoreq. 260,000. Similarly, DLK transiently expressed in COS 7 cells autophosphorylated in vivo and migrated at approx. 260 kDa when sepd. by nonreducing SDS-PAGE. In cotransfection expts., FLAG-tagged DLK or a FLAG-tagged truncated DLK mutant (F-.DELTA.520) was coimmunopptd. with Myc-tagged DLK and formed complexes under nonreducing conditions consistent with the conclusion that DLK formed covalently assocd. homodimers in overexpressing COS 7 cells. In aggregating neuronal-glial cultures, depolarization of plasma membrane lead to dephosphorylation of DLK. Treatment of aggregates with 5 nM or 200 nM okadaic acid lead to a shift in electrophoretic mobility consistent with phosphorylation of DLK. Treatment with cyclosporin A, a specific **inhibitor** of the calcium/calmodulin-dependent protein phosphatase 2B (calcineurin), had no effect on DLK phosphorylation under basal conditions. However, cyclosporin A completely **inhibited** DLK dephosphorylation upon membrane depolarization.

L3 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 7
AN 1996:471167 CAPLUS
DN 125:163044
TI Genetics of responses to morpholine-type fungicides and of avirulences in Erysiphe graminis f. sp. hordei
AU Brown, James K. M.; Boulaire, Stephanie Le; Evans, Neal
CS Cereals Research Department, John Innes Centre, Norwich, NR4 7UH, UK
SO European Journal of Plant Pathology (**1996**), 102(5), 479-490
CODEN: EPLPEH; ISSN: 0929-1873
PB Kluwer
DT Journal
LA English
AB The genetics of the responses of the barley powdery mildew pathogen, Erysiphe graminis f.sp. hordei, to three morpholine-type fungicides were studied. Resistances to a phenylpropylamine fungicide, fenpropidin, and to a morpholine, fenpropimorph, co-segregated in crosses of a sensitive isolate, DH14, with each of two resistant ones, CC151 and CC152. In the cross CC151 .times. DH14, the results were consistent with resistance to

both fungicides being controlled by a single gene, at a locus named Fen1. In the other cross, CC152 .times. DH14, the genetics of resistance were more complicated; the data were consistent with the segregation of two complementary, unlinked genes which each conferred resistance to both fungicides. Fenpropidin-resistant progeny of CC151 .times. DH14 were significantly more resistant to fenpropimorph than were fenpropidin-resistant progeny of CC152 .times. DH14, although the resistant progeny of the two crosses did not differ significantly in their level of fenpropidin resistance. Fenpropidin-resistant progeny of CC151 .times. DH14 were significantly more resistant to another morpholine, tridemorph, than were fenpropidin-sensitive progeny, but this was not the case for CC152 .times. DH14. Resistance to triadimenol, a C14 demethylation-**inhibitor** (DMI) fungicide, segregated in both crosses. Triadimenol resistance appeared to be controlled by one gene in each cross and was not assocd. with morpholine resistance. CC151 .times. DH14 also segregated for eight avirulence genes. Two of these matched the Mla6 resistance, while one gene matched a previously unknown resistance in a Pallas near-isogenic line, P17, which also carries a known resistance gene, **Mlk**. Fen1 was not significantly linked to the triadimenol resistance gene, Tdl(a), or to any of the eight avirulence genes. Avra61, Avra12, AvrLa, AvrP17 and Tdl(a) were linked, as were Avra10 and Avrk.

L3 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2003 ACS
AN 1999:134644 CAPLUS
DN 130:140228
TI Polyethylene light-converting film
IN Sun, Xinshi; Ma, Ciguang; Li, Zhifen; Ning, Xun
PA Xinsangda Economy and Tech. Consultation Co., Ltd., Qingdao, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 11 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CN 1122814	A	19960522	CN 1994-114161	19941107 <--
	CN 1052493	B	20000517		
PRAI	CN 1994 114161		19941107		

OS MARPAT 130:140228
AB The light converting film which converts UV into orange red comprises polyethylene 100, light converting agent Men+XmYn-**mLk** 0.1-5.0, where Me = Eu, Tb; X, Y = Cl-, NO3-, COO-, diketone anion; L = 2,2'-bipyridine, phenanthroline, 1-vinyl benzimidazole; n = 2, 3; m = 0, 1, and k = 0, 1, 2, 3, aging-**inhibiting** additive 0.1-1.0, and antifogging agent (fatty acid ester of polyol) 0.5-1.0 parts. The film was used in green house, showing a temp. increase in winter and decrease in summer, and decreased crop mature period for 3-15 days.

L3 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2003 ACS
AN 1984:196797 CAPLUS
DN 100:196797
TI Increasing the corrosion resistance of reinforcements
AU Tobolich, V. V.; Krasnyuk, V. A.; Opekunov, V. V.; Zholdakov, A. A.; Gorbachev, Yu. A.
CS USSR
SO Stroitel'nye Materialy i Konstruktsii (**1983**), (4), 16
CODEN: SMKOD5; ISSN: 0136-7773
DT Journal
LA Russian
AB The addn. of .gtoreq.0.3 wt.% modified lignosulfonates M-1 [66418-81-3], M-4 [89591-78-6], and **MLK**-1 [89591-93-5], based on cement, as plasticizers to concrete mixes with cement-sand ratio 1:(1-3) improved the flow properties of the mix, increased the strength and water- and frost-resistance of the hardened concrete, and decreased corrosion of St.

3 reinforcement to 0.001-0.002 mm/yr. vs. 0.002 without the plasticizer and 0.002-0.003 with the plasticizer SDB. In the presence of 1 wt.% setting accelerators SN [89592-30-3] and KhK [80940-32-5], 0.5 wt.% lignosulfonate slowed corrosion to 0.001-0.002 and 0.03-0.05 mm/yr., resp., vs. 0.005 and 0.03, resp., without plasticizer and 0.001 and 0.05 with SDB.

L3 ANSWER 10 OF 17 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1993:54980 BIOSIS
DN PREV199395031282
TI Interaction of berbamine compound E-6 and calmodulin-dependent myosin light chain kinase.
AU Hu, Zhuo-Yi (1); Gong, Yue-Shong; Huang, Wen-Long
CS (1) Div. Biochem., China Pharmaceutical Univ., Nanjing, Jiangsu 21009 China
SO Biochemical Pharmacology, (1992) Vol. 44, No. 8, pp. 1543-1547.
ISSN: 0006-2952.
DT Article
LA English
AB The interaction of the berbamine compound E-6 and calmodulin (CaM)-dependent myosin light chain kinase (MLCK) has been studied. The experimental results showed that the **inhibition** of **MLK** activity was increased with increasing amounts of E-6 and was overcome completely by the addition of excessive CaM. The stimulatory activity of MLCK induced by CaM was gradually **inhibited** by the increasing concentrations of compound E-6, showing that the **inhibition** of MLCK activity by compound E-6 was concentration dependent; and the K-i was 0.95 mu-M. Compound E-6 diminished the fluorescence intensity of dansyl-labeled CaM and the intensity was increased gradually by the addition of different amounts of CaM. Compound E-6 had no effect on the activity of MLCK fragments produced by limited trypsinization, and it is a novel and considerably potent calmodulin antagonist.

L3 ANSWER 11 OF 17 Elsevier BIOBASE COPYRIGHT 2003 Elsevier Science B.V.
AN 1997201536 ESBIOBASE
TI **Mixed lineage kinase** (**MLK**)-1 is differentially expressed in beta cell lines and regulates in vitro growth and differentiation
AU DeAizpurua H.J.; Cram D.S.; Naselli G.; Devereux L.; Dorow D.S.
CS H.J. DeAizpurua, Burnet Clinical Research Unit, W. and E. Hall Inst. Med. Research, Royal Melbourne Hospital, Parkville, Vic. 3050, Australia.
SO Experimental and Clinical Endocrinology and Diabetes, (**1997**), 105/4 (A24-A25), 0 reference(s)
CODEN: ECEDFQ ISSN: 0947-7349
DT Journal; Conference Article
CY Germany, Federal Republic of
LA English

L3 ANSWER 12 OF 17 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 97:490313 SCISEARCH
GA The Genuine Article (R) Number: XG017
TI Decreased potassium stimulates bone resorption
AU Bushinsky D A (Reprint); Riordon D R; Chan J S; Krieger N S
CS UNIV ROCHESTER, SCH MED, DEPT MED, NEPHROL UNIT, 601 ELMWOOD AVE, BOX 675, ROCHESTER, NY 14642 (Reprint)
CYA USA
SO AMERICAN JOURNAL OF PHYSIOLOGY-RENAL PHYSIOLOGY, (**JUN 1997**) Vol. 41, No. 6, pp. F774-F780.
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ISSN: 0363-6127.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Metabolic acidosis induces net calcium efflux (J(Ca)(+)) from cultured bone, in part, through an increase in osteoclastic resorption and a decrease in osteoblastic formation. In humans provision of base as potassium (K+) citrate, but not sodium (Na+) citrate, reduces urine Ca (U-Ca), and oral KHCO3 decreases bone resorption and Uc, in postmenopausal women. Potassium deprivation alone leads to an increase in U-Ca. To determine whether decreased extracellular K+ concentration ([K+]) at a constant pH, P-CO2, and [HCO2-] alters J(Ca)(+) and bone cell activity, we measured J(Ca)(+), osteoblastic collagen synthesis, and osteoclastic beta-glucuronidase release from neonatal mouse calvariae cultured for 48 h in medium of varying [K+]. Calvariae were cultured in control medium (approximate to 4 mM [K+]) or medium with mildly low K+ (**MLK**, approximate to 3 mM: [K+]), very low K+ (VLK, approximate to 2 mM [K+]), or extremely low K+ (ELK, approximate to 1 mM [K+]) (n greater than or equal to 9 in each group). Compared with control, ELK, but not **MLK** or VLK, resulted in a marked increase in J(Ca)(+) and an increase in beta-glucuronidase release and a decrease in collagen synthesis. J(Ca)(+), was correlated directly with medium beta-glucuronidase activity and inversely with collagen synthesis. To determine whether the reduction in medium [K+] was associated with a decrease in intracellular pH (pH(i)), we measured pH(i) in MC3T3-E1 cells, a mouse osteoblastic cell line. Incubation in 1 mM [K+] led to a significant decrease in pH(i) compared with 3 mM [K+]. Thus incubation in a reduced [K+] medium stimulates J(Ca)(+) and osteoclastic enzyme release and **inhibits** osteoblastic collagen synthesis, which may be mediated by a reduction in bone cell pH.

L3 ANSWER 13 OF 17 CROPU COPYRIGHT 2003 THOMSON DERWENT
AN 1988-82745 CROPU F
TI Frequencies of Virulence and Fungicide Resistance in the European Barley Mildew Population in 1985.
AU Limpert E
LO Freising Weihenstephan, Ger.
SO J.Phytopathol. (119, No. 4, 298-311, 1987) 8 Fig. 3 Tab. 22 Ref. (AJU) CODEN: JPHYEB
AV Technische Universitaet Muenchen, Lehrstuhl fuer Pflanzenbau und Pflanzenzuechtung, D-8050 Freising-Weihenstephan, West Germany.
DT Journal
LA English
FA AB; LA; CT
AN 1988-82745 CROPU F
AB Random samples of spores of Erysiphe graminis f. sp. hordei were taken over important barley growing areas in Europe and tested in the laboratory for their virulence on the following resistant varieties:- Igri (Ml 41/145), Union (Mgl), Carina (Mla6+Mlg), Vada (MlLa), Ortolan (Mla7+**Mlk**), Sultan (Mla12), Sewa (Mla3), Gitte (Mla1+, Welam (Mla9), Atem (Mlo+MlLa) and Rupal (Mla13+M Ru3). For fungicide resistance, each isolate was tested on Igri treated with either triadimenol (6, 13.4, 71.7, 164, 375 mg/kg) or fenpropimorph (2.35, 4.7, 9.4, 18.8, 37.5, 75 mg/kg). Frequency and level of resistance against triadimenol showed significant regional differences and were generally correlated with the intensity of fungicide use. Against fenpropimorph, similar levels of sensitivity were observed in different parts of Europe.
ABEX A correlation between the sensitivity of isolates and the intensity of fenpropimorph use was not established. Virulence frequencies mostly showed regional differentiation. The results are discussed with respect to current and previous conditions of cultivations, to the spread of the pathogen by wind and towards strategies for more effective use of host resistance and of fungicides.

L3 ANSWER 14 OF 17 CROPU COPYRIGHT 2003 THOMSON DERWENT
AN 1985-85091 CROPU F
TI Dynamics of Triazole Sensitivity in Barley Mildew, Nationally and Locally.

AU Wolfe M S; Minchin P N; Slater S E
LO Trumpington, U.K.
SO Proc.Br.Crop Prot.Conf.Pests Dis. (2, 465-70, 1984) 1 Fig. 3 Tab. 10 Ref
CODEN: PBCDDQ
AV Plant Breeding Institute, Trumpington, Cambridge CB2 2LQ, England.
DT Conference
LA English
FA AB; LA; CT
AN 1985-85091 CROPU F
AB Dynamics of triazole e.g. triadimenol (T) sensitivity in barley mildew (Erysiphe graminis f.sp. hordei) were surveyed nationally and locally. From 1981-84 the population of mildew on barley in England became increasingly less susceptible to triazole fungicides. Individual field surveys of winter barley untreated and treated with T showed differences in the frequency of pathogen genotypes sensitive and insensitive to the fungicide which were most evident in the autumn. Populations in the treated fields became more sensitive by the following spring probably due to selection; those in the untreated fields became less sensitive probably due to immigration, so that inter-field differences became less evident. In the treated fields, the sensitive and insensitive fractions of the pathogen population showed a distinct spectrum of pathogenicity characters.
ABEX During 1983/84, individual field surveys were made in 5 winter barley fields, 3 of which were treated with T seed dressing. A WIST (wind impaction spore trap) survey was made using susceptible barley cv. Golden Promise. Greenhouse-grown seed was untreated or treated with 0.025-0.125 g a.i. T/kg seed. Seedlings were exposed at 1st leaf for 50 km sections of a standard 200 km route to the E and S of Cambridge. Colonies were counted after 7-8 days incubation. 5 Separate fields of winter barley (2 Maris Otter and 1 Tipper treated with T and 2 of Tipper untreated) with sampled between Oct 1983 and July 1984. Pots of untreated Golden Promise were dragged between rows of the crops to give spore deposition. Single colonies were isolated for tests in detached leaves of seedlings grown from seed treated at 0.025-0.375 g a.i. T/kg seed (0.375 is recommended). Isolates were tested on differential varieties Julia (Mlg), Hassan (Mla12), Midas (Mla6), Lofa (Mlv), and Ark Royal, AR (**Mlk** -Mla7). The general trend to T insensitivity of pathogen population continued (up to the 1st 6 mth of 1984). Pathogen was largely insensitive to 0.025 g a.i. T/kg. This pattern was widespread on other routes. ED50 values of single colony isolates were classed as sensitive (S), intermediate and insensitive (IS). In early autum there were more IS isolates in treated fields but with time the difference between treated and untreated diminished. Pathogenicity of all differentials, except AR, was higher among IS than S isolates e.g. Lofa. Pathogenicity for AR was high in S but absent in IS isolates.

L3 ANSWER 15 OF 17 CABA COPYRIGHT 2003 CABI
AN 97:131423 CABA
DN 971410048
TI Decreased potassium stimulates bone resorption
AU Bushinsky, D. A.; Riordon, D. R.; Chan, J. S.; Krieger, N. S.
CS Department of Medicine, University of Rochester School of Medicine, Rochester, New York 14642, USA.
SO American Journal of Physiology, (**1997**) Vol. 272, No. 6, pp. F774-F780. 32 ref.
ISSN: 0002-9513
DT Journal
LA English
AB To determine whether a decreased extracellular K+ concentration ([K+]) at a constant pH, PCO2 and [HCO-3] alters net calcium efflux (J+Ca) and bone cell activity, J+Ca, osteoblastic collagen synthesis and osteoclastic beta -glucuronidase release from neonatal mouse calvariae (frontal and parietal bones of the skull) cultured for 48 h in medium of varying [K+] were measured. Calvariae were cultured in control medium (equivalent to 4 mM [K+]) or medium with mildly low K+ (**MLK**, equivalent to 3 mM

[K+]), very low K+ (VLK, equivalent to 2 mM [K+]) or extremely low K+ (ELK, equivalent to 1 mM [K+]) (nmore than or equal to 9 in each group). Compared with control, ELK, but not **MLK** or VLK, markedly increased J+Ca and increased beta -glucuronidase release and a decrease in collagen synthesis. J+Ca was correlated directly with medium beta -glucuronidase activity and inversely with collagen synthesis. To determine whether the reduction in medium [K+] was associated with a decrease in intracellular pH (pHi), pHi were measured in MC3T3-E1 cells, a mouse osteoblastic cell line. Incubation in 1 mM [K+] significantly decreased pHi compared with 3 mM [K+]. Thus incubation in a reduced [K+] medium stimulated J+Ca and osteoclastic enzyme release and **inhibited** osteoblastic collagen synthesis, which may be mediated by a reduction in bone cell pH.

L3 ANSWER 16 OF 17 CANCERLIT
AN 81692882 CANCERLIT
DN 81692882
TI DEVELOPMENT OF NK ACTIVITY DURING IN VITRO CULTURE.
AU Bolhuis R
CS Rotterdam Radiotherapy Inst., Rotterdam, The Netherlands.
SO Non-serial, **(1980)** Natural Cell-Mediated Immunity Against Tumors. Herberman RB, ed. New York, Academic Press, 1321 pp., 1980. .
DT Book; (MONOGRAPH)
LA English
FS Institute for Cell and Developmental Biology
EM 198102
ED Entered STN: 19941107
Last Updated on STN: 19960517
AB The characteristics of the different types of cytotoxic cells generated after mixed lymphocyte culture (MLC; cytotoxic T lymphocytes, CTL and MLC-natural killer cells, MLC-NK) were compared and related to those of 'fresh' NK cells and killer (K) cells. The allogeneic lymphocytes (A.B.) MLC-generated NK cell activity was approx equal to that induced by the pool of lymphocytes of 20 allogeneic individuals (A.C.); thus, the amount of different major histocompatibility complex antigens expressed by the stimulator cell population was of minor importance for the induction of MLC-NK cells. The rate of cell proliferation was not a crucial factor in this induction. The immunologic specificity of CTL effector cells was demonstrated. Heat-inactivated mononuclear lymphoid cells did not **inhibit** the MLC-generated NK cell lysis of target cells of the K-562 erythroleukemic cell line. Both K-562 and T24 bladder carcinoma cells sometimes **inhibited** the specific lysis of A.B. or A.C. CTL against B lymphoid target cells. It was suggested that this **inhibition** was due to the phytohemagglutinin-induced susceptibility to lysis of lymphoblasts by MLC-NK cells. The results obtained in the cross cold target cell **inhibition** assay of cell-mediated lysis indicated that the target cells structures for lysis on tumor MLC-NK cells were different from the CD determinant for CTL on lymphocytes. K-562 **inhibited** the lysis of T24 targets as efficiently as T24, but T24 was a less effective **inhibitor** of K-562 target cell lysis than K-562 cells, indicating the specificity of the reaction. MLC-NK cells lysed human T24 and mouse P-815 mastocytoma and GRSL mouse mammary tumor cells (as shown in a 4-hr 51Cr-release assay), whereas fresh NK cells did not, indicating that the target cell spectrum of **MLK**-NK cells is broader than that of fresh NK cells and that the MLC-NK cells represent the de novo generation of previously inactive progenitor cells that are present in human peripheral blood. (30 Refs)

L3 ANSWER 17 OF 17 PASCAL
AN 1997-0377128 PASCAL

TIEN Decreased potassium stimulates bone resorption
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CS Nephrology Unit, Department of Medicine, University of Rochester School of Medicine, Rochester, New York 14642, United States

SO American journal of physiology. Renal physiology, **(1997)**, 41(6), F774-F780, 32 refs.
DT Journal
BL Analytic
CY United States
LA English
AV INIST-670F, 354000067332580120

AB Metabolic acidosis induces net calcium efflux (J.sub.C.sub.a.sup.+) from cultured bone, in part, through an increase in osteoclastic resorption and a decrease in osteoblastic formation. In humans provision of base as potassium (K.sup.+) citrate, but not sodium (Na.sup.+) citrate, reduces urine Ca (U.sub.C.sub.a), and oral KHCO.sub.3 decreases bone resorption and U.sub.C.sub.a in postmenopausal women. Potassium deprivation alone leads to an increase in U.sub.C.sub.a. To determine whether decreased extracellular K.sup.+ concentration ([K.sup.+]) at a constant pH, PCO.sub.2, and [HCO.sub.3.sup.-] alters J.sub.C.sub.a.sup.+ and bone cell activity, we measured J.sub.C.sub.a.sup.+, osteoblastic collagen synthesis, and osteoclastic .beta.-glucuronidase release from neonatal mouse calvariae cultured for 48 h in medium of varying [K.sup.+]. Calvariae were cultured in control medium (4 mM [K.sup.+]) or medium with mildly low K.sup.+ (**MLK**, 3 mM [K.sup.+]), very low K.sup.+ (VLK, 2 mM [K.sup.+]), or extremely low K.sup.+ (ELK, 1 mM [K.sup.+]) (n >= 9 in each group). Compared with control, ELK, but not **MLK** or VLK, resulted in a marked increase in J.sub.C.sub.a.sup.+and an increase in .beta.-glucuronidase release and a decrease in collagen synthesis. J.sub.C.sub.a.sup.+was correlated directly with medium .beta.-glucuronidase activity and inversely with collagen synthesis. To determine whether the reduction in medium [K.sup.+] was associated with a decrease in intracellular pH (pH.sub.i), we measured pH.sub.i in MC3T3-E1 cells, a mouse osteoblastic cell line. Incubation in 1 mM [K.sup.+] led to a significant decrease in pH.sub.i compared with 3 mM [K.sup.+]. Thus incubation in a reduced [K.sup.+] medium stimulates J.sub.C.sub.a.sup.+ and osteoclastic enzyme release and **inhibits** osteoblastic collagen synthesis, which may be mediated by a reduction in bone cell pH.

=> log y

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